



Characteristics of New Oxygen-Carrying Plasma and Its Application Prospects in the Treatment of Severe Acute Pancreatitis

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Abstract

Oxygen-carrying plasma, a new type of colloid substitute, is composed of Hydroxyethyl Starch (HES) and acellular Hemoglobin-Based Oxygen Carriers (HBOCs). It can supplement colloidal osmotic pressure and rapidly improve the body's oxygen supply. The resuscitation effect of the new oxygen-carrying plasma in animal shock models is better than that of HES or HBOC alone. It can reduce the histopathological damage and mortality associated with severe acute pancreatitis, and it is expected to become an interesting treatment method for severe acute pancreatitis. This article reviews the characteristics of the new oxygen-carrying plasma, its role in fluid resuscitation, and its application prospects in the treatment of severe acute pancreatitis.

Keywords: New oxygen-carrying plasma; Fluid resuscitation; Severe acute pancreatitis; Hydroxyethyl starch; Hemoglobin-based oxygen carriers

Background

Fluid resuscitation is one of the most important methods in the treatment of clinical emergency and critical illness, and it is the key to the treatment of patients in shock. In recent years, the role of colloid in fluid resuscitation in severe acute pancreatitis has been increasingly attracting greater attention. As a plasma substitute, Hydroxyethyl Starch (HES) has the characteristics of low price and easy storage. Studies have found that HES not only can increase the colloid osmotic pressure and improve perfusion [1] but can also reduce inflammation and protect organs [2]. However, the risk of kidney damage with the use of HES is high [3] Table 1. Hence, research on acellular hemoglobin carriers has increased. Hemoglobin-Based Oxygen Carrier (HBOCs), which uses human hemoglobin as raw materials, has advantages because it has no risk of infectious diseases, does not need blood type matching, and can be easily stored and transported; thus, HBOCs have always been a research hotspot in blood substitutes and oxygen therapeutics [4-6]. Although HBOCs supplement effective circulating blood volume and increase tissue oxygen supply, but they also have side effects such as blood vessel contraction [7] (Table 2). Researchers at the Concord Institute of Blood Transfusion Institute of Blood Transfusion in China investigated a new type of oxygen-carrying plasma. The new oxygen-carrying plasma has the expansion effect of regular plasma, which can promptly restore blood perfusion to tissues, remove the accumulated metabolites in the body, and restore exchange in the interstitial matter. In addition, the oxygen carried by the oxygenated plasma is transported to the tissues, which quickly restores the oxygen supply to the tissues and improves the hypoxic state [8-11]. Hence, the new oxygen-carrying plasma is expected to reduce the side effects caused by the use of HES or HBOC alone and compensate for each other's deficiencies. This article reviews the characteristics of the new oxygen-carrying plasma and its role in fluid resuscitation and targeted restoration of effective circulating blood volume after the occurrence of severe acute pancreatitis in order to prevent and improve the immune and inflammatory effects of severe acute pancreatitis.

New Oxygen-Carrying Plasma

The new oxygen-carrying plasma is a combination of HES and Polymerized Human Cord Hemoglobin (PolyCHb), a type of HBOC. HES is mainly composed of high-molecular-weight amylopectin; meanwhile, HBOCs are nanoscale erythrocyte substitutes that are prepared by covalently cross-linking, polymerizing, and chemically modifying purified hemoglobin for oxygen transport and release [5]. PolyCHb, which has an average molecular weight of 200 kDa, is a mixture

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Table 1: The advantages of hydroxyethyl starch.

Author	Publication time/country	Study design	Study population/objects	Number of study population
Rittoo D [12]	2005/England	Clinical Trial	Patients	40
Makiko Komori [1]	2019/USA	Animal Trial	Rabbits	44
Hongliang Zhao [14]	2020/Switzerland	Animal Trial	Rats	288

Data are from Rittoo D [12], Makiko Komori [1], Hongliang Zhao [14]

Table 2: The advantages and disadvantages of HBOCs.

	Author	Publication time/country	Study design	Study objects	Number of study population
Advantages	Kai Bachmann [18]	2014/United States	Animal Trial	Pigs	39
	Jing Zhao [19]	2017/United States	Animal Trial	Rats	18
	Li Wang [20]	2017/United States	Animal Trial	Rats	32
Disadvantages	Alayash AI [23]	2014/Netherlands			
	Gladwin MT [22]	2017/United States			

Data are from Kai Bachmann [18], Jing Zhao [19], Li Wang [20], Alayash AI [23], Gladwin MT [22]

Table 3: Proposal and research on a new type of oxygen-carrying plasma.

Author	Publication time/country	Study design	Study object	Number of study population
Kai Bachmann [18]	2014/United States	Animal Trial	Pigs	39
Yan Dong [26]	2015/China	Animal Trial	Rats	30
JiANG Bingyu [11]	2016/China	Animal Trial	Rats	40

Data are from Kai Bachmann [18], Yan Dong [26], JiANG Bingyu [11]

of polymers formed by cross-linking glutaraldehyde with purified human cord hemoglobin with a molecular weight of 32 kDa (Table 3).

Characteristics of HES

HES, an artificial colloid widely used in clinical practice, can stabilize the hemodynamics of patients in shock, improve microcirculation perfusion, and increase tissue oxygen supply [1]. At the same time, it has anti-inflammatory properties [12] and can reduce capillary leakage [13]. The use of HES in sepsis not only expands the volume but also reduces the adhesion molecules in the circulatory system, thereby reducing the activity and damage of vascular endothelial cells [14]. Studies have also shown that HES can reduce organ damage caused by systemic inflammation and damage caused by ischemia and reperfusion [15]. The use of HES can improve the microcirculation of the pancreas, reduce the levels of interleukins 1 and 8 in the early stage of severe acute pancreatitis, shorten the duration of fluid balance positivity, and protect the patient's immune status and renal function [16]. However, its use has some limitations, such as its inability to supplement oxygen for hypoxic tissues or improve the balance of oxygen supply and demand in organs and circulation in a timely manner. Thus, Chengmin et al. [17] proposed a combination of HBOCs and HES, each of which has specific functions, to create a new generation of colloidal plasma substitutes with both expansion capacity and oxygen-carrying function.

Characteristics of HBOCs

HBOCs do not have AB0 antigen and can be used for all blood types without antigen detection [18]. As the functional diffusion distance between red blood cells and endothelium is reduced, oxygenation is allowed even in areas of vascular stenosis or vasoconstriction where red blood cells cannot penetrate [19,20]. Therefore, this function may prevent the progression of tissue necrosis. In addition, compared with normal human hemoglobin, HBOC has a lower affinity for oxygen, which improves tissue oxygenation [21]. However, previous studies have found that HBOCs have side effects, such as oxidative stress, vascular activity, coagulation dysfunction, and nephrotoxicity

[22,23]. To reduce the side effects of HBOCs, researchers have conducted a series of animal experiments to determine the suitable dosage and application time. A study found that infusion of PolyHb is beneficial in maintaining the average arterial pressure and heart rate of rats and in alleviating tissue hypoxia. It can correct acidosis, and low PolyHb concentrations can reduce the oxidative stress caused by it and reduce lipid peroxidation damage [24]. Furthermore, PolyHb can reduce heart, lung, and kidney damage and improve mesenteric circulation [25]. Regarding the coagulation disorder of PolyHb, some researchers used different concentrations of PolyHb in volunteers and found that it does not intensify coagulation dysfunction [10]. HBOCs are currently in the third phase of clinical trials and are expected to be widely used in clinical practice in the future.

Characteristics of the new oxygen-carrying plasma

The continued research and development of new oxygen-carrying plasma in experimental and clinical studies is a new starting point and motivation for the field itself, which has attracted many researchers. Dong et al. [26] conducted animal experiments on the curative effect of the new oxygen-carrying plasma and found that it can effectively maintain the average arterial pressure of rats and can better relieve metabolic acidosis in rats than using HES alone. They also found that plasma generation after increasing the oxygen-carrying function significantly improved the quality of life of rats compared with existing plasma. Jiang et al. [11] applied a new type of oxygen-carrying plasma to animal shock models and found that it has a vascular expansion effect similar to HES and can improve the microcirculation disorder caused by hemorrhagic shock in rats. The effect of restoring the partial pressure of tissue oxygen at the initial stage of shock resuscitation in rats is better than that of HES, and it can also improve the survival rate of shocked rats. Peipei et al. [27] investigated the effects of the new oxygen-carrying plasma on intestinal ischemia-reperfusion in rats with hemorrhagic shock and found that adding PolyHb to the HES solution can improve tissue oxygen supply and acidosis and reduce intestinal tissue ischemia-reperfusion injury. In an experiment to determine the stability of the

new oxygen-carrying plasma during the storage period, Chen Gang et al. [17] observed that Ascorbic Acid (AA) can effectively control methemoglobin but has no significant effect on the oxygen-carrying component HBOCs. Furthermore, AA was proven to have a good effect on the antioxidation and storage stability of novel colloid plasma substitute's solution. Some researchers reported that the combination of HES and acellular hemoglobin can improve the microcirculation in severe acute porcine pancreatitis, thereby reducing histopathological damage and mortality [18]. The new oxygen-carrying plasma is currently in the laboratory test verification stage and is expected to undergo further clinical trials for clinical application.

Application Prospects of the New Oxygen-Carrying Plasma in the Treatment of Severe Acute Pancreatitis

Pathogenesis of severe acute pancreatitis

The course of severe acute pancreatitis can be roughly divided into three stages [28]: (1) Acute reaction period, which is characterized by a systemic inflammatory response, often accompanied by major complications such as shock, acute respiratory distress syndrome, acute renal failure, and acute encephalopathy; (2) systemic infection period, which is characterized by pancreatic or peripancreatic necrosis infection, which can easily develop into sepsis, with multiple organ dysfunction or dual infection as its main clinical manifestation; (3) residual infection period, during which systemic malnutrition is the main clinical manifestation, with the presence of the posterior peritoneum or residual cavity in the abdominal cavity. Often, because of poor drainage, the sinus tract would not heal for a long time, and it would be accompanied by a digestive fistula. If the local inflammation of severe acute pancreatitis is effectively controlled and the local necrotic tissue is not infected, the course of the disease may not enter the infection period, and it will be directly preceded to the recovery period in approximately 2 weeks. Combined with the early pathophysiological characteristics of severe acute pancreatitis, severe acute pancreatitis usually starts with local non-infectious inflammation, and systemic inflammatory response will soon appear. Inflammatory cells gather at the site of pancreatic injury and are activated. The damaged pancreas produces and releases a large number of interleukins and chemokines, which directly act on pancreatic macrophages and circulating inflammatory cells, including neutrophils, lymphocytes, and macrophages. Endothelial cells promote the expression of adhesion molecules in the microcirculation of the pancreas and lungs. Large amounts of inflammatory substances enter the blood circulation, promoting the release of a variety of inflammatory factors, and the chain amplification effect appears, resulting in tissue and cell damage. This leads to immune damage, systemic inflammatory syndrome, and multiple organ failure. In addition, excessive inflammatory response and massive release of inflammatory cytokines aggravate the damage to systemic tissues and organs. Changes in circulatory function in acute severe pancreatitis are characterized by abnormal blood distribution [29]. Under the action of inflammatory cells, the circulation capacity not only becomes absolutely insufficient due to local exudation, ascites, vomiting, etc., but also becomes relatively insufficient due to abnormal expansion of blood vessels. Finally, severe pancreatitis can also cause an increase in the permeability of the lung microcirculation and extravasation of substances in the blood vessels, which can cause acute lung injury.

Secondary abdominal cavity infections and increased abdominal pressure further aggravate the insufficient perfusion of organs and

tissues in the abdominal cavity. Therefore, early fluid resuscitation and adequate tissue oxygen supply are important links in the prevention and treatment of multiple organ dysfunction syndromes in patients with severe acute pancreatitis. In the early stage of severe acute pancreatitis, pancreatic necrosis and hemorrhage cause rapid loss of effective capacity, and at the same time, capillary permeability increases significantly, causing capillary leakage. A large amount of fluid is transferred from the blood vessel to the interstitial space, the effective circulating blood volume is drastically reduced, and tissues become edematous. Prompt correction of hypovolemia and hypoxemia can help maintain oxygen delivery and avoid or reduce damage to organ function caused by tissue hypoperfusion. However, in the early stage of severe acute pancreatitis, interstitial edema and capillary leakage caused by increased vascular endothelial permeability make fluid resuscitation more difficult.

Effect of the new oxygen-carrying plasma on severe acute pancreatitis

HES can reduce the early pro-inflammatory cytokines, the risk of intra-abdominal hypertension, and the use of mechanical ventilation in patients with severe acute pancreatitis [16,30]. After infusion of bovine hemoglobin in rats with severe pancreatitis, pancreatic microcirculation was improved and tissue damage was reduced [31]. HBOC infusion in the animal model of severe acute pancreatitis does not increase the production of oxygen free radicals [32]. Adding HBOC-200 to HES can improve pancreatic microcirculation in rats, and the additional oxygen supply (HBOC-200) did not increase the occurrence of lipid peroxidation [32]. The use of HES plus HBOC-301 for fluid resuscitation in a porcine acute pancreatitis model was found to improve the microcirculation of severe acute porcine pancreatitis, thereby reducing histopathological damage and mortality [18]. At present, there are few studies on the effects of a new oxygen-carrying plasma on severe acute pancreatitis.

Discussion

Fluid supplementation is the most critical step in the treatment of severe acute pancreatitis. Timely correction of hypovolemia and hypoxemia can help maintain oxygen delivery and avoid or reduce organ function damage caused by tissue hypoperfusion. However, excessive supplementation with the crystal fluid tends to aggravate tissue edema, pulmonary edema, hypoxemia, intestinal edema, abdominal hypertension, and intestinal dysfunction. Therefore, the combination of crystals and colloids can be used for fluid resuscitation in severe acute pancreatitis. At present, the commonly used colloids in clinical practice include plasma, albumin, and colloidal substitutes such as HES and dextran. Since plasma and albumin are mostly allogeneic infusions, there is a risk of allergies, thus requiring cross-matching and increasing the loss of patients' hemoglobin; furthermore, the cost is high. In the search for a better resuscitation plan, researchers have successively explored the functions and mechanisms of HES and HBOCs.

HES has been used clinically as a cheap colloid substitute, as it inhibits the accumulation of red blood cells in blood vessels and improves microcirculation [33]. In recent years, there have been reports on the harmful effects of HES on the kidneys and the side effects of coagulopathy. A study found that the harmful effects can be reduced by controlling the dose [34]. A large study comparing crystal drugs and HES showed that the incidence of renal dysfunction in the HES group was significantly lower than that in the saline group [35,36]. Regarding the side effects of artificial colloids in patients

with coagulation dysfunction, data on the use of a major abdominal surgery fluid supplement showed that only dextran can significantly increase the risk of bleeding. This risk can be prevented by controlling the amount of HES [13].

PolyCHb has oxygen-carrying and oxygen-releasing functions similar to those of red blood cells, which can improve the oxygen supply of hypoxic tissues and reduce tissue cell damage caused by ischemia and hypoxia [37]. PolyCHb with a low concentration of hemoglobin (20 g/L) can provide oxygen to ischemic and hypoxic tissues and organs in a timely and effective manner and reduce tissue cell damage caused by ischemia and hypoxia [10]. Its high oxygen affinity, low viscosity, and small average diameter allow it to be used freely in the microcirculation and transport of oxygen to hypoxic tissues. PolyCHb has been proven to be beneficial to multiple organs during shock, including the heart [38], liver [9], lungs [39], and kidney [7].

To effectively expand the volume and improve the oxygen supply in a timely manner and to compensate for the limitations and side effects of HES and HBOCs, researchers have developed a new type of oxygen-carrying plasma and analyzed its therapeutic effect and protective effect on organs in an animal model of hemorrhagic shock [40]. Studies have also shown that the application of HES and acellular hemoglobin can improve the microcirculation of severe acute porcine pancreatitis, thereby reducing histopathological damage and mortality [18]. These effects may be achieved by effectively expanding the volume using HES and providing oxygen, restoring the nitroso-redox balance, reducing mitochondrial oxidative damage, and reducing the inflammatory response caused by reperfusion using cell-free hemoglobin.

Limitations and Prospects

Both HES and acellular hemoglobin carriers have been used in clinical resuscitation fluids. Research on new oxygen-carrying plasma is still preliminary; most are focused on hemorrhagic shock, and very few studies are focused on severe acute pancreatitis. Moreover, its application in human disease states lacks the verification of long-term, multicenter clinical randomized controlled trials. In recent years, more attention has been paid to research on new oxygen-carrying plasma resuscitation, but its specific mechanism of action requires further study. Although the new type of oxygen-carrying plasma has been found to effectively supplement colloidal osmotic pressure as well improve the surrounding oxygen supply and reduce the application value of inflammatory response, its application in clinical practice needs in-depth research.

The intestine is one of the key organs injured by severe acute pancreatitis. After ischemia, the intestinal tract releases pro-inflammatory molecules, such as superoxide anion free radicals and cytokines, causing the intestinal flora to shift and enter the portal vein and systemic circulatory system, leading to intestinal remote organ failure [41,42]. A study has shown that HES-130 infusion inhibits the release of pro-inflammatory cytokines, such as tumor necrosis factor α and interleukin 6 [43], which may be the reason for the improvement in intestinal barrier dysfunction [44-46]. Our new type of oxygen-carrying plasma can be used for the treatment of severe acute pancreatitis through the mechanism of HES by improving intestinal oxygen metabolism, reducing the release of inflammatory mediators, and protecting the integrity of the intestinal barrier. Reducing the body's oxidative stress and inflammation while

reducing the translocation of intestinal bacteria, combined with PolyHb, can increase the oxygen supply of the intestinal mucosa and other important organs and its synergistic effect in improving the mesenteric microcirculation [19,20]. This process prevents further development of severe acute pancreatitis, thereby reducing the occurrence of MOF, which is an important step in the treatment of severe acute pancreatitis. In addition, we found that the current research on new oxygen-carrying plasma does not involve the pathway level. Earlier studies have shown that HES reduces inflammation and inhibits the Nuclear Factor kappa B (NF- κ B) signaling pathway [47]. In a recent study of severe pancreatitis, systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome in mice developed in parallel, but they can be reduced by NLRP3 inhibition [48-50]. The NLRP3/NF- κ B pathway may be involved in this pathway [51]. We speculate that the new oxygen-carrying plasma used to reduce severe acute pancreatitis may inhibit the NLRP3/NF- κ B pathway. Although the clinical application of the new oxygen-carrying plasma still has issues, it is foreseeable that as the research on the new oxygen-carrying plasma progresses, its clinical application will become clearer and its application areas will also be more extensive, not only supplementing the effective circulating blood volume and improving the body's oxygen supply but also providing a therapeutic effect on patients with severe acute pancreatitis.

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