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REVIEW

Treatment of hyperbilirubinemia with blood purification in China

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Abstract

The incidence of hyperbilirubinemia is high clinically, which is difficult to cure by medication, surgery or interventional therapies. Non-bioartificial liver is the main alternative in the blood purification for hyperbilirubinemia, which includes plasma exchange, hemoperfusion, hemodialysis, molecular adsorbent recycling system and so on. The research results and clinical experiences in China show that these methods are effective in lowering high levels of bilirubin with fewer side effects. The hyperbilirubinemias of different causes, with different complications or accompanying different diseases can be treated by different methods. Bioartificial liver, hybrid artificial liver support system and adsorbent membrane material have also been studied and their development in reducing hyperbilirubinemias has been achieved. This article gives a brief overview on the actuality and research improvement in blood purification for hyperbilirubinemia in China.

Key words: Hyperbilirubinemia; Blood purification; Treatment; China; Review

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INTRODUCTION

Hyperbilirubinemia, namely jaundice, is a common clinical manifestation, and it may be life threatening. Many diseases result in hyperbilirubinemias, some are refractory, and cannot be cured by medication or surgery. Though some obstructive jaundice related to the common bile duct can be relieved quickly and temporarily with the recent development of interventional therapies, there is a paucity of effective methods for those lesions occurring in small or capillary bile ducts such as primary biliary cirrhosis of the liver, and for some other hyperbilirubinemias that need to be cured in a short time such as an obstructive jaundice that cannot be relieved or does not have an indication for operational or interventional therapy temporarily, an acute or chronic hepatic failure, a portal hypertension associated with serious icterus in liver cirrhosis and a quite severe jaundice before liver transplantation. So, how to reduce the high concentration of bilirubin in the blood of these patients has always been a focus of study for many researchers. Blood purification has been used for treating hyperbilirubinemia in the recent two decades, and it is also called non-bioartificial liver (non-BAL) for distinguishing bioartificial liver (BAL), a recent research hotspot. Non-bioartificial liver could temporarily improve the status of patients with end-stage liver diseases and help by extending time and increasing opportunity for further treatment despite lack of synthesis and metabolic function. Especially at present when research of the artificial liver is still at its initial phase in China, non-bioartificial liver is applied widely and further research is being performed for higher efficacy. In this paper, reports by Chinese researchers on these aspects are reviewed.

APPLICATION AND CURATIVE EFFECT OF BLOOD PURIFICATION FOR DEPRESSING HIGH LEVEL OF BILIRUBIN

Non-bioartificial blood purification applied in China currently includes plasma exchange (PE), hemoperfusion (HP), hemodialysis (HD), molecular adsorbent recycling system (MARS)[1], of which PE is used most frequently.

Plasma exchange (PE)

In the process of PE, plasma is separated and discarded, while cells, as well as some supplied albumin, plasma and balance solution are reinfused back so as to remove the causative agents. PE not only removes bilirubin, endotoxin and complement activator, but also replenishes albumin, coagulation factor and hepatic regenerative stimulating substance, which can correct metabolic disorder.

Shang *et al*[2] compared treatments in two different groups: 116 patients with chronic severe hepatitis and

hepatic failure were categorized as a therapy group with 142 instances of blood purification using an artificial liver support system (ALSS, 800 PE) and medication therapy; 118 patients with the same illnesses as mentioned above were categorized as a control group which was given only supportive care and observed. All cases were consistent with virus hepatitis diagnostic criteria enacted at the China Virus Hepatitis Conference in 2000 (2000CVHC). After treatment, total bilirubin (TBIL) decreased 62.96% in the therapy group, and the clearance rate was much higher than that in the control group. The statistical difference was significant. Ming *et al*[3] also treated 32 cases of severe hepatitis diagnosed according to 2000CVHC by PE (HP200 blood purification equipment, YT-50PP PE, Yatai Company, Ningbo, China; plasma separation rate, 20-30 mL/min; blood flow rate, 60-100 mL/min; infused fresh plasma, 2000 mL), and the result showed TBIL descended 25.17%, icterus faded and symptoms improved. PE could alleviate hyperbilirubinemia, decrease mortality, and prolong survival time. However, by use of PE, large amounts of fresh plasma are consumed and there is a paucity of safety issues such as hepatitis, HIV, anaphylaxis and other complications addressed for regulatory approval. Zou *et al*[4] utilized Plasauto IQ PE instrument (OP-08W plasma segregator) for 116 times in 93 patients with severe hepatitis (consistent with 2000CVHC). After treatment, the short-term total effective rate was 80.2% (93/116), 51 were cured, 18 died, and 24 were discharged from hospital. During the treatment, adverse reactions occurred in 64 patients including erythema in 24 (22.41%), hypotension in 21 (1.72%), anesthesia accompanied hemifacial spasm in 15 (12.93%) and alimentary tract hemorrhage in 2, both of whom died, one died of intracranial hemorrhage. Besides, the drop of serum bilirubin level after PE treatment might rise again. Even so, PE is still a relatively mature method. Yang *et al*[5] reported that in the treatment of viral hepatitis hyperbilirubinemia, fewer amounts and more numbers of albuminpheresis could decrease hyperbilirubinemias more effectively in refractory hepatitis, especially in Types non-B and non-C. Meanwhile it could avoid blood contamination, providing a relative security. Long-term effects with low incidence of adverse reaction were confirmed.

HP

The accurate meaning of hemoperfusion is blood adsorption, i.e., pathogenic medium dissolved in the blood is adsorbed to a solid matter with an ample surface for removing various toxins in a perfusion apparatus. Based on blood or plasma flowing through the perfusion apparatus, blood perfusion or plasma perfusion was named. Blood perfusion is rarely used clinically because the adsorbent may hurt or activate blood cells, so usually plasma perfusion is used for hemoperfusion. There is no incidence of cross infection, protein susceptibility or other side effects because fresh plasma, albumin and other blood products do not need to be supplied in the process of hemoperfusion. There are mainly two kinds of adsorbents used in hemoperfusion, activated charcoal and resin. Activated charcoal, is a kind of broad-spectrum adsorbent, which can effectively clear endotoxin, leukocyte inhibitory factor, cytotoxin of inhibition liver cell regeneration agent, aromatic amino acid, hydroxybenzene, indole and short chain fatty acids, and also can availably adsorb bilirubin in the blood[6]. Clinically resin is used more frequently than activated charcoal. Sorbents are macroreticular resins including uncharged resin and ion exchange resin. Although the adsorption capacity of resin is inferior to that of activated charcoal, it has a higher clearance rate towards all kinds of lipophilic and hydrophobic substances such as bile acid, bilirubin, free fatty acid and amine. Du *et al*[7] treated 2 cases of severe obstructive jaundice with carcinoma in pancreas head by HB-H-6 resin (Liver and Gall Disease Research Center, the Third Center Hospital of Tianjin, China) before surgery. TBIL, direct bilirubin (DBIL) and indirect bilirubin (IBIL) decreased more than 340 μmol/L, 230 μmol/L and 98 μmol/L, respectively. Bilirubin adsorption in the perfusion was at the highest speed from 15 to 45 min. HB-H-6 resin consisted of macroporous anion exchange resin and cation exchange resin. Anion adsorbed IBIL while cation adsorbed DBIL. Two patients were bridged successfully to surgery on the following day. It indicated that perfusion by HB-H-6 is safe and effective as a bridging option for malignant obstructive jaundice during the waiting time for transplantation. Zhang *et al*[8] identified bilirubin binding capacities of ten different kinds of resin (Tianjin Jinlin Biochemistry Development Company, China) and found that the clearance rates of both resins No.5 and No.9 towards DBIL were more than 70%; however, resin No.9 was superior to resin No.5 in regard to IDBIL. It indicated that No.9 had the best bilirubin removal efficiency among the ten kinds of resins, and No.5 was next to it. Resin No.9 had polyvinyl alcohol as a matrix and amino acid as a ligand, while No.5 was constituted by polystyrene resin and polar reactive groups coupled on it. Among the ten kinds of resin with pretreatment for the experiments of bilirubin adsorption in a solution, only one kind was selected, which had a higher capacity for bilirubin removal, constituted by hydrophilic crosslinked polyvinyl alcohol matrix, and amino acid as a ligand. The clearance rates of TBIL and DBIL in the solutions were 68.16% and 58% respectively, and those of TBIL and DBIL were 68% and 70% in the sera of patients. Furthermore, its blood compatibility was superior. In addition, resin could adsorb molecules with a molecular weight between 500 and 5000 Daltons, which covered the molecular weight of bilirubin, 548.67 Daltons. Accordingly, HP could treat hyperbilirubinemia effectively, and showed an applicable foreground[9].

HD

As a safe and simple technique of blood purification, HD has been applied extensively in renal failure. Dialysis means the solute passing through a semipermeable membrane from high concentration to low in solution, which includes the movement of solute and water. A routine application of HD cannot effectively clear a high concentration of serum bilirubin. It has been reported that the clearance rate could be raised using plasma as the dialysate or associated with other purification methods. In the report by Liu *et al*[10], 21 cases of

hyperbilirubinemias received different alternatives: high volume hemofiltration, HE (HP200 blood purification equipment, YP-50PP membrane type plasma separator, Yatai Company, Ningbo, China; total amount of plasma exchange, 3000-3600 mL; plasma exchange rate, 25-30 mL/min; displacement with homeotype fresh refrigerated plasma), MARS (ALSS-MARS, Germany; blood flow, 150 mL/min; time of treatment, 6 h) and hemodialysis with plasma-based dialysate (HD-PBD) (AV600 filter, Diapact CRRT, CVVHD mode; blood flow, 250 mL/min). After treatment, the clearance rates of TBIL were 19.1%, 39.9%, 36.6% and 38.2%, respectively, while that of DBIL were 2.7%, 41.0%, 33.9% and 28.5%. The results indicated that there were no significant differences among HD-PBD, PE and MARS in removals for TBIL, DBIL, serum ammonia and bile acid. Lin *et al*[11] treated 26 severe hepatitis patients with a combination of PE and high-flow hemodiafiltration (HDF), there was obvious improvement of symptoms, with 49.46%, 48.77% and 47.98% decrease in levels of TBIL, DBIL and ammonia with low incidences of severe hemorrhage, shock or other complications. The common adverse effect was still hypersensitivity to plasma. You *et al*[12] treated 8 cases of severe hepatitis complicated with renal failure by a combined therapy of hemoperfusion and hemodialysis (330 mL HA blood perfusion equipment coupling F6 blood dialyzor; F-4008E Hemodialysis machine, Germany; carbonic acid dialysate; blood flow, 200-220 mL/min; dialysate flow, 500 mL/min; time of treatment, 4-5 h), and the patients had good tolerance with a decrease of TBIL by 15.6%-45.8% and no severe complications occurred.

Molecular adsorbent recycling system (MARS)

MARS is composed of an albumin recycling system, activated charcoal or resin, dialysis and so forth. It combines blood purification techniques of HD and a molecular adsorbent to selectively clear lipophilic albumin-bound toxin and hydrosoluble toxin. It can also adjust water and electrolyte disturbance, as well as acid-base disequilibrium. Yang *et al*[13] treated 30 patients with chronic severe type B hepatitis by MARS (MARS equipment, AKLIN Company, Germany; AK95 hemdialysis machine, Jinbo Company, China). The diagnosis of each patient was consistent with revised criteria at a Beijing academic conference in 1995, and their TBIL and DBIL were 369.77 ± 112.17 μmol/L and 114.75 ± 38.98 μmol/L, respectively. The levels lowered to 293.19 ± 99.16 μmol/L and 95.00 ± 31.41 μmol/L and symptoms of patients were improved after treatment of MARS. Chen *et al*[14] reported 28 patients with acute or chronic liver failure, who received 56 intermittent MARS treatments (Teraklin, Germany; time of therapy, 6-8 h) based on medicinal treatment, the TBIL, DBIL and total bile acid decreased by 31.47%, 29.15% and 35.91%, respectively after a single treatment of MARS, and the process was smooth except one ended having acute upper gastrointestinal bleeding; 8 cases of hypokalemia were corrected in time by infusing kalium intravenously. In Sun's study on treatment of 27 patients with severe hepatitis (the diagnosis was consistent with 2000CVHC) by MARS, he evaluated the degree of severity of disease by the MELD system[15,16], and reported that MARS could effectively alleviate hyperbilirubinemia, cure hepatorenal syndrome and decrease mortality obviously. Anyhow, MARS is an effective alternative for acute or chronic liver failure and their complications.

COMPARISON AND SELECTION OF BLOOD PURIFICATION METHODS FOR REDUCING BILIRUBIN

The research of non-bioartifical liver is relatively mature and it is safe and easy to gain ground. Based on medicinal treatment, the hyperbilirubinemias caused by different pathogenic factors should be treated by different blood purification methods, or by a combination of these methods according to the accompanying symptoms, complications, concomitant diseases, existing equipment and conditions as well. Liu *et al*[1] treated 161 cases of severe hepatitis or liver failure with different blood purifications. The results indicated that PE(variant homeotype plasma exchange; 2000-2500 mL plasma; plasma segregating rate, 25-30 mL/min; blood flow, 30-40 mL/min), HP(microcapsule activated charcoal perfusion column; total time, 1.5-3 h) and MARS (NCU-11 blood dialysis machine and MARS mainframe, Germany) could reduce TBIL by 46.53%, 21.20% and 37.69% respectively, and blood ammonia by 19.04%, 15.35% and 44.13%. PE showed a superior ability in removing bilirubin, and at the same time it could supply albumin, coagulation factors and other biological active substances. MARS reduced blood ammonia effectively, so it would be a good option for patients complicated with hepatic encephalopathy to reduce icterus and correct hepatic coma simultaneously. Patients who had ascites and renal failure could be treated by HD. HP was able to correct alkalosis and hypokalemia, so it could be applied to patients with these complications. In addition, combination of MARS, PE, HP and HD can treat abdominal dropsy and renal inadequacy[11,12]. Recently it was reported that PE (SP1 or SP2, Fresenius Company), HP (BR-350, Asahi Company; Japan) and HD could be used in combination. Firstly, PE was performed (blood flow ⩽ 100 mL/min), subsequently bilirubin was adsorbed. Excessive water was dialysed out in those patients with complicating hepatorenal syndrome or being infused with redundant water during PE[17].

RESEARCH FOCUS AND ADVANCEMENT OF BLOOD PURIFICATION FOR CLEARING BILIRUBIN

The study of bioartificial liver is a new hotspot recently. The so-called bioartificial liver is loaded with a combination of liver, tissues, cells and other things that are obtained from homologous or heterogeneous animals with special materials and equipment. It simulates the main functions of the liver: detoxification, synthesis and regulation[18]. Liver cells form a crucial part of BAL, and the cell type that can be used on humans is limited. It includes normal adult hepatocytes, fetus stem cells, liver tumor cells, swine hepatocytes, human stem cells,

reversible immortalized hepatocytes and so on[19]. Several liver support systems have been described, but no system has gained widespread clinical acceptance[20]. Chen *et al*[21] used a high concentration of L-02 human hepatocytes (Shanghai Institute of Biochemistry and Cell Biology, China) into hollow fiber bioreactor(YT-PP/F50 grate Ⅱ plasma separator, Yatai Company, Ningbo, China) and constituted extracorporeal BAL with another assisting circulation device. An extracorporeal-circulation test was performed later and the effect on bilirubin was observed simultaneously. The result showed that TBIL decreased by 35.78% after 4 h of treatment. Heterogenic or heterologous hepatocytes and tumor cells of liver cultured *in vitro* are used in BAL, so it has risks of xenogenic rejection, potential xeno-zoonosis and morbigenous. The hollow fiber bioreactor was also given attention because of its vital function for containing hepatocytes in BAL. The limitation of cultured cells substituting natural livers and the culture techniques, as well as the limitation of large-scale production, preservation and transportation of biologic materials make it difficult for BAL to be popularized clinically.

Recently, the combination of non-BAL and BAL was proposed, namely hybrid ALSS. It consisted of plasma separator, activated charcoal adsorber, level detector, attemperater and hollow fiber bioreactor and so on[22]. Li *et al*[23] used hybrid ALSS (Chinese experimented small porcine, Experiment Animal Research Center of Beijing Agriculture University; D-hanks perfusate and TECA- Ⅰ hollow fiber bioreactor, USA) to treat 15 chronic severe hepatitis patients (the diagnosis was consistent with 2000CVHC) and found that hybrid ALSS had an effect of reducing bilirubin. The TBIL decreased 240 μmol/L while DBIL decreased 110 μmol/L after treatment. Ten patients improved and were discharged from the hospital and one case was bridged to transplantation successfully and is living till now. Although 4 cases died, cure rate and survival rate of severe hepatitis had already increased without severe complications. Hybrid ALSS will be improved constantly with the development of ALSS. Consequently, for the time being the application of non-BAL is still the main alternative as a clinical treatment method for hyperbilirubinemia.

Though the technology of blood purification has improved gradually, a great deal of problems still exist. The main problems include low removal efficiency, long therapeutic time and expensive treatment costs. One key limitation of PE is bulk supplement of plasma and costly price, while the single application of HD is rare because of its low clearance. Further improvement and study on HP and MARS was brought into a focus by modified adsorbent materials. The ideal method of solving these vital problems is using the best membrane material and an optimally modified method, and increasing removal efficiency to the best advantage. Many scholars in the world are further groping for membrane modification for specific adsorption based on investigating bead affinity adsorbents. Yu *et al* immobilized guanidine on cross-linked polyvinyl alcohol gel, and coated cyclodextrin and glucose to polymer for adsorbing bilirubin in the blood[24-26]. At present, the most advanced affinity membrane is CA/PEI affinity membrane. The basic component of the membrane-cellulose acetate (CA) has favorable blood compatibility. Wei *et al*[27] used cellulose acetate as a compatible membrane matrix and made polylysine and quaternary ammonium salt as a ligand to prepare two kinds of modified affinity membranes after grafting. It was used to remove bilirubin from the HSA solution. Polyethyleneimine (PEI) has been widely used in the field of biochemistry and medicine now. CA/PEI membrane could be used directly to clear endotoxin or adsorb heavy metal[28,29], to prepare a metal chelating affinity membrane, to further covalently link other specific ligands on the membrane, and to work out a modified affinity membrane that could possess better adsorption performance for bilirubin in serum. Otherwise, favorable immune compatibility, i.e., ability to reduce immunoreaction was a precondition of the biomaterial being applied in clinics[30]. Now it is known that structure character of material is related to activating rejection of body fluid, cell and host[31]. Peng *et al*[32] evaluated the immunocompatibility of propylene-acidamide grafted polypropylene membrane (PP-g-AAm) *in vitro* on peripheral blood mononuclear cells (PBMCs) and confirmed that PP-g-AAm had preferable immunocompatibility.

Blood purification for hyperbilirubinemia is not an etiological therapy but strives for the opportunity to cure. So many patients can obtain surgery and liver transplantation finally. With the development of medicine, molecular biology, biochemistry and chemical engineering, blood purification will improve continuously and will make new breakthroughs for treatment of hyperbilirubinemia.

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