Blood exchange transfusion in fulminant hepatitis in a small infant: a case report

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ABSTRACT

Objectives: To report blood exchange transfusion in acute liver failure following hepatitis B infection.

Setting: Infectious Disease Department of Children's Hospital No.2 in Ho Chi Minh City, Vietnam.

Design: A descriptive case report.

Patient: A 3.5 months old baby boy was admitted to the hospital with a presentation of progressively worsening jaundice for one month. The patient was diagnosed with hepatitis B

infection with a positive HBV DNA quantitative assay. Plasma exchange was indicated in the view of progressive liver failure and gradually increasing hepatic coma. However, it was impossible to perform plasmapheresis in this case because the patient was small (in terms of age and weight) and there was no suitable plasma exchange filter. Accordingly, the patient was treated with 3 times of blood exchange transfusion in combination with the antiviral drug, lamivudine. After each blood exchange transfusion, the biochemical values (bilirubin, liver enzymes and coagulation profile) gradually improved and he was discharged after 1 month of treatment.

Conclusion: Blood exchange transfusion is an effective treatment in acute liver failure and should be considered in cases where plasma exchange is not possible (as the patient is too small) or equipment is not available.

Introduction

Acute liver failure (ALF) or fulminant liver failure (FLF) is a potentially reversible clinical syndrome characterized by severe hepatocellular dysfunction with the onset of coagulopathy (international normalized ratio (INR) ≥ 1.5) and encephalopathy (any degree of altered mental status) occurs within eight weeks of the first symptom in the absence of preexisting liver disease or cirrhosis[1,2]. In 1993, O'Grady *et al*. subdivided ALF into hyperacute, acute, and subacute depending on the time interval between the appearance of jaundice and the onset of encephalopathy based on data from King's College[3]. The term *hyperacute* is used when the onset of encephalopathy occurs within 7 days of the appearance of jaundice, *acute* is used for patients

who develop altered mental status between 7 and 21 days of onset of jaundice while *subacute* is used when encephalopathy occurs between 21 days and 26 weeks of the onset of jaundice[3]. This classification provides us the clues of the cause of disease, possible complications, and suitable management in ALF[3].

The causes of ALF vary demographically, including viral infection, drugs or toxins induced, metabolic causes, autoimmune disorders and vascular causes[1,2,4–6]. Viral infection is predominant in the developing countries while in the West, the most common cause of ALF is due to drug-induced liver injury, often from acetaminophen[2]. However, the etiology of a large proportion of cases are remained unknown, despite intensive investigation[2].

A thorough search for underlying etiology is undertaken once the diagnosis of ALF is confirmed[1]. Apart from that, understanding the complications which may be present, including renal failure, circulatory dysfunction, coagulopathy, gastrointestinal bleeding, encephalopathy, cerebral edema, and metabolic disturbances is essential in the management of ALF. Management of ALF includes treatment of the underlying etiologies if present, intensive supportive care, management of complications, and orthotopic liver transplantation (OLT), in which OLT is the standard therapy for patients with irreversible liver damage[4,7]. The overall survival of ALF has improved to sixty percent with it[4]. However, the availability of OLT is limited hence, alternative bridging therapy should be used to gain time until a suitable donor organ is found.

Plasma exchange is a procedure in which the patient's blood is removed and replaced with the packed red cells with fresh frozen donor plasma. It has clinically endeavored for the treatment of acute liver failure with a survival rate of 40% compared to 20–25% with supportive therapy since 1970[8]. Plasma exchange help to eliminate toxins that are bound to albumin as well as free toxins such as aromatic amino acids, ammonia, endotoxins, indols, mercaptans, phenols that are

contributing to liver encephalopathy, hyperactivity syndrome, decreased systemic vascular resistance and decreased cerebral perfusion. A recently published randomized controlled trial (RCT) 2016 demonstrated a mortality benefit in patients with ALF who was given plasma exchange without liver transplantation[9]. However, it requires an appropriate plasma replacement filter device and specialized highly trained medical personnel.

Exchange blood transfusion which has the same mechanism with plasma exchange can be considered as an alternative. According to the Fulminant Hepatic Failure Surveillance Study from Boston, Massachusetts in the year 1968, treatment of 284 stage 4 hepatic coma patients from ninety-eight centers has been reported. 101 of them did not have any exchange transfusion and the survival was 9.9 % while 166 of them who received an exchange transfusion has a survival rate of 24.1 %[1].

In this case, we would like to introduce a case in which blood exchange transfusion was used to treat acute liver failure caused by hepatitis B virus in a patient who is unable to perform a plasma exchange.

Case report

A 3.5 months old male baby from Binh Phuoc Province, Vietnam, with no previous history of liver disease was admitted to the hospital after one month of progressively worsening jaundice (This case report was generated after the patient was discharged from the hospital, so we could not get an informed consent). On physical examination, it was noted that the patient was jaundice in looking. However, his vital signs were stable, and there were no other signs of chronic liver disease and no distention of jugular venous vein. His cardiopulmonary examination was normal.

On abdominal examination, his liver was palpable 2 cm below the right costal margin, soft in consistency and tender. There was no ascites noted.

Laboratory tests showed (Table 1) severe hepatocellular necrosis with alanine aminotransferase (ALT) 2982 UI/L, aspartate transaminase (AST) 1366 UI/L. Furhtermore, cholestasis was observed with increased total and dominant direct bilirubin (660/407 µmol/L), and with alkaline phosphate 1067 U/L and gamma-glutamyltransferase (GGT) 191 U/L. In addition, coagulopathy was present with prothtrombine time (PT) 39.6s and international normarized ration (INR) 3.16.On the other hand, blood glucose was 67 mg/dL, with normal electrolytes, and the renal functions were not impaired with the increased levels of NH_3 in the blood 115 µmol/L. Moreover, alpha-1 antitrypsin was normal recording 155.7 mg/dL. In addition, normal abdominal ultrasound examination. Also, tests for microbiological etiologies were performed (HBsAg, Hepatitis A and C and Epstein-Barr virus IgM, IgG antibodies, TORCH Infections, Dengue, *Chlamydia*, *Mycoplasma pneumonia* IgM). The results showed that IgM antibodies were positive for the agents: HBsAg, CMV, Herpes Simplex virus, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*. The quantitative assay for HBV DNA was 4600 UI/mL (3.66 log10). No documented poisoning, defect of metabolism or excessive use of acetaminophen.

The patient was diagnosed with acute hepatic failure caused by acute hepatitis B and was treated with vitamin K, lactulose, and fluid restriction with monitoring and correction of blood glucose. Moreover, specific treatment of acute hepatitis B infection begins with lamivudine 8 mg/kg/day.

During the first week of hospitalization, the patient was hemodynamically stable and showed no neurological manifestations, but the liver functions gradually deteriorated with progressive hyperbilirubinemia, elevated serum NH_3 and progressive coagulation disorder (Table 1). On the 8^{th} day of hospitalization, the patient demonstrated signs of grade 2-3 hepatic encephalopathy

with drowsiness and decreased awareness. He has not improved with standard treatment. Hepatic coma worsened gradually (grade II – III) and the patient was indicated for plasma exchange. The hospital had two filters of two different sizes, Primaflex TPE 1000 and TPE 2000 sets (Baxter, USA). Accordingly, bearing in mind that the patient is small, it was not possible to perform a plasma exchange (even with the TPE 1000 available which required priming techniques that were not available at the time), so a blood exchange transfusion was performed instead.

Table 1. Clinical and laboratory characteristics of the patient during treatment.

Date of admission	**D1**	**D7**	**D9 (1st transfusion)**		**D12 (2nd transfusion)**		**D14 (3rd transfusion)**		**D20**	**D41**
			Before	**After**	**Before**	**After**	**Before**	**After**		
Total bilirubin (μmol/L)	253.6	577	660	286	362	168	175	93	214	129.3
Direct bilirubin (μmol/L)	151	334	407	98.5	182	82	69.6	35.6	132	96.2
AST (U/L)	2982	139	138	107	104	60	112	45	119	210
ALT (U/L)	1366	177	119	43	53	22	30	16	54	148
NH_3 (μmol/L)	115	91			139		103		51	
PT (s)	39.6	85.6	70.4	22.7	40.4	29.7	35.6	22.7	23.1	18.1
aPTT (s)	45	82.5	73.1	38.8	127.1	52.5	44.8	42.4	42.1	36.8
Fibrinogen (g/L)	0.87	0.4	0.4	1.84	1.27	1.59	1.33	1.76	1.47	1.78
INR	3.16	7.16	5.82	1.76	3.23	2.33	2.83	1.76	1.78	1.39
Platelets ($\times 10^3$/mL)	100		147	78	74.3	30.7	65	47.7	102	103
Coma level	I	II	III	III	II	I	I	I	alert	alert

After each blood exchange transfusion, the mental status of the patient gradually improved (Coma grade 0)[10], and the biochemical values (bilirubin, liver enzymes and coagulation profile) gradually returned to normal (Table 1). On the other hand, NH_3 improved (91,139,103 μmol/L), but did not return to normal within the third week when the liver functions started to recover (51 μmol/L) (Table 1). Futhermore, PT showed significant improvement after each blood transfusion returning to its lower-most value in D41 (Table 1). Complications of blood transfusion such as hyperglycemia, electrolyte disorders, cardiac arrhythmia, and hypothermia were not observed in this patient. Thrombocytopenia was noted after each blood exchange transfusion because only red blood cells and fresh plasma were transfused (Table 1). However, there were no clinical manifestations of bleeding.

After 3 times of exchange transfusion, the mental status of the patient gradually improved, the patient was alert, and could communicate physically and react with his parents. Moreover, one episode of pneumonia responded to antibiotic treatment and the patient was discharged after about 1 month of hospitalization. HBV DNA concentration improved and was 286 UI/ml at discharge (2.46 log10). Furthermore, the patient continued to receive lamivudine treatment and was followed-up every month.

Discussion

“Acute liver failure” is defined as severe, reversible liver damage associated with hepatic encephalopathy within eight weeks of the first symptom to appear with no history of liver diseases[11]. Most of the current definitions recognize the difference between phenotypes and determine the period at which the onset of the first symptom until encephalopathy occurs. Causes of acute liver failure include acetaminophen overdose, prescription of certain drugs, herbs abuse,

hepatitis viruses, and other organisms, poisoning, autoimmune disease, hepatic vascular disease, cancer, shock, and other causes. Treatment includes intensive supportive care, treatment of the underlying cause if present, and early liver transplantation. Special attention has to be given to liver coma, fluid adjustment, hemodynamics, metabolism and infection control[4]. Specific treatment may be effective, depending on the cause. Treatment should be initiated early and carefully with frequent monitoring for disease progression, besides, careful evaluation is necessary to prevent any delay or failure of liver transplantation[1,2,5].

For fulminant liver failure with low self-recovery ability, the standard treatment is supportive care for the liver as a bridging therapy for liver transplantation. Plasma exchange is a non-cell-based liver support therapy recommended with a high level of evidence. Plasma exchange help eliminate toxins that are bound to albumin as well as free toxins such as aromatic amino acids, ammonia, endotoxins, indols, mercaptans, phenols and other factors related to liver coma, hyperactivity syndrome, decreased systemic vascular resistance and decreased cerebral perfusion. Recent research shows that it is important to eliminate inflammatory mediators by the plasma replacement technique[12]. Plasma exchange is mainly used as a temporary solution for liver transplantation[12]. However, this method requires an appropriate plasma replacement device and trained medical personnel.

Blood exchange transfusion has been practiced in the treatment of acute liver failure for years and a lot of cases have shown favorable outcomes. A study reported the first case of recovery from hepatic coma after two exchange blood transfusion in a boy aged 13[13]. Another study reported that six recoveries out of twelve patients were treated with blood transfusion[14]. In the same year, another recovery from acute hepatic failure after exchange transfusion in a 25 year-old patient was reported[15]

Plasma exchange therapy is commonly used as bridging therapy in acute liver failure. A recently published randomized controlled trial (RCT) 2016 demonstrated a mortality benefit in patients with ALF who was given plasma exchange without liver transplantation[9]. The procedure is generally safe as the risk for life-threatening events such as death, hemolysis, hypotension is low, ranging between 0.025% to 4.75% although the incidence of all complications peaks to 40%[16,17]. As the most serious complication in this procedure, death has an incidence of 0.05%, however, most of them were with severe pre-existing medical conditions[18]. Hence, this procedure has to be performed carefully to avoid any possible serious complications.

In low-birth-weight infants (<6 kg), the plasma replacement filter is not suitable, and the procedure must be performed in the intensive care unit environment because of the potential of serious side effects. An alternative, which is not less effective but perhaps safer, is a manual total blood transfusion. Blood exchange transfusion is used for the treatment of some diseases, mainly jaundice due to blood group incompatibility in the newborn, sickle cell anemia and some metabolic disorders, toxic corn. The general risk is the same as for any blood transfusion procedure, with some occurring more frequently in infants, such as heart failure, hypothermia, hypocalcemia, hyperkalemia and hypoglycemia[19–21].

Mechanism of exchange blood transfusion is similar to that of plasma exchange, which includes removal of bilirubin, bile salts, endotoxins, and cytokines and addition of coagulation factors and antibodies. The procedure for extracellular detoxification, using polymeric plasma absorption, is very useful in animal models with liver failure[22]. The use of activated carbon absorption is beneficial in the early stages of coma (52.6% survival rate; control 31.6%), while the use of activated carbon combined with resin BR-601 (aimed at eliminating bilirubin and bile acids), improves survival rate by 63.1%. The addition of a third combonent of polymyxin B (eliminating

endotoxins) absorption systems furtherly improved the survival rate to 73.3%. These animal experiments support the notion that plasma detoxification improves survival in acute liver failure[22]. It is important to note that blood transfusion is less effective at reducing blood ammonia (as can be clearly seen in this case), while continuous dialysis can remove this substance quickly within hours[22,23].

There is currently no data on the prognosis of blood exchange transfusion in acute liver failure. Transfusion has been reported in some cases and clinical reports of acute hepatic failure that have been widely accepted. According to SJ Saunder, from Cape Town, an adult study in 1968, most of the adult patients responded to the technique, 11 out of 22 patients fully recovered and 6 patients still living healthy[24]. Furthermore, it has been reported that 3 cases of acute liver failure due to sepsis were treated with whole blood transfusion by DG Harendra de Silva, showing positive results, when only one patient developed metabolic acidosis after blood transfusion due to citrate anticoagulation[25].

In the absence of means to perform liver transplantation procedure, we recommend performing blood exchange transfusion in acute liver failure until self-recovery of the liver functions or liver transplantation is available.

Moreover, people with fulminant hepatitis, severe acute hepatitis, and prolonged acute hepatitis may benefit from nucleoside analogs treatment. Lamivudine, adefovir, entecavir, and tenofovir are considered acceptable options, while interferon is contraindicated[26]. Furthermore, nucleoside analogues treatment is recommended, but no optimal duration of which is known. Treatment should last until HbsAg is negative in the patient's serum, or at least 3 months after HBsAg seroconversion, or 1 year after HBeAg seroconversion and HbsAg remained positive[26,27].

Conclusion

The causes of acute liver failure should be determined once the diagnosis is made. Treatment includes intensive supportive care, treatment of the underlying cause, and early identification of a liver transplant recipient. Special attention should be given to liver coma, such as fluid management, hemodynamics, metabolism and infection control. Blood exchange transfusion procedure may be useful in patients with fulminant hepatitis in cases where plasma exchange is not possible. This is supportive management while waiting for the recovery of liver function or liver transplantation.

Conflict of interest

All authors declare no conflict of interest related to this work.

Author contributions

Each author took part in the design of the study and participated in writing and reviewing the manuscript and all agree to accept equal responsibility for accuracy of this paper.

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