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CASE REPORT

Alternating therapeutic plasma exchange (TPE) with double plasma molecular adsorption system (DPMAS) for the treatment of fulminant hepatic failure (FHF)

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Abstract

Alternating therapeutic plasma exchange with double plasma molecular adsorption system can rapidly remove bilirubin and ammonia and supplement the essential substance from the blood, which could be used as an effective treatment for fulminant hepatic failure.

KEYWORDS

double plasma molecular adsorption system, extracorporeal blood purification, fulminant hepatic failure, therapeutic plasma exchange

1 | INTRODUCTION

Fulminant hepatic failure (FHF), also known as acute liver failure (ALF), is a rare life-threatening disease with a high mortality rate, presenting with encephalopathy, jaundice, coagulopathy, and an imbalanced immune system, regardless of its etiology. ALF is most widely defined as an abnormal international normalized ratio (INR) of greater than or equal to 1.5 and any degree of encephalopathy in a patient without preexisting underlying chronic liver disease.[1] But some exceptions to the definition of FHF are patients with Wilson disease, acute presentation of autoimmune hepatitis (AIH), or Budd-Chiari syndrome, which can all present with FHF even if there is some degree of underlying chronic liver disease. These patients are treated as having FHF rather than acute-on-chronic liver failure(ACLF).[2] Liver transplantation seems to be an "ideal" treatment in FHF, however, subject to scarcity of donor livers or disqualification for medical or other reasons.[3] Therefore, in the last few decades, many efforts have been made to develop treatments, using either a biological[4,5] or non-biological (cell-free) form[6–9] to address this problem for liver failure patients. Considering the intricate functions of the liver, including detoxification, biosynthesis, and regulation, a biological artificial liver support system that incorporates liver tissue or cells would be preferred

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to replace the liver. But in reality, non-biological artificial liver (NBAL) is the most mature technique and is used more frequently in clinical practice. In FHF, various kinds of toxins are overproduced. In order to remove these toxins, extracorporeal blood purification (EBP) can be used, such as dialysis, adsorption, and conventional plasma exchange. Therapeutic plasma exchange (TPE) is a fundamental and simple EBP. TPE replaced with fresh frozen plasma (FFP) can substitute the liver for some functions, because it could nonspecifically remove the medium- and macro-molecule metabolic toxins (minus), and meantime supplement the essential substances such as albumin and coagulation factors (plus) that FHF patients lack.[10] Based on bilirubin adsorption therapy, the double plasma molecular adsorption system (DPMAS) is employed through combination of two kinds of adsorbents, including broad-spectrum adsorption column (HA330-II) and specific adsorbent for bilirubin (BS330). Previous study showed that, in ACLF patient, compared with DPMAS, TPE could reduce bilirubin more effectively, but was accompanied by a higher albumin loss.[11] DPMAS combined with PE could have a more favorable short-term prognosis.[12] At present, NBAL studies mostly focus on ACLF whereas there are scarce reports in FHF patients. In this paper, we present a case to highlight the importance of alternate TPE and DPMAS for treatment of FHF and compare the clearance efficiency.

2 | CASE PRESENTATION

A 49-year-old male presented at our hospital with chief complaint of jaundice, dark urine for 2 years, and skin rash 2 months ago. Autoimmune markers showed positive anti-nuclear antibody (ANA) with a titer of 1:100. He was performed liver biopsy two years ago, and the pathology reports confirmed the diagnosis of autoimmune hepatitis (AIH) in another hospital. Then, prednisone (Pre) and mycophenolate mofetil (MMF) were prescribed to control disease. Two months ago, he began to suffer from skin rash, interfering with his sleep tremendously. Previous treatments, such as prednisone (Pre) and mycophenolate mofetil (MMF), seemed to lose their effects. Jaundice was not relieved by ursodeoxycholic acid and adenosylmethionine butanedisulfonate. On the second hospital day, he developed hepatic coma. Laboratory tests were compatible with hepatic failure and showed total bilirubin, 1301 μmol/L (reference range, <17 μmol/L); conjugated bilirubin, 897 μmol/L (reference range, <5 μmol/L); albumin (Alb), 28.7 g/L (reference range, 40–55 g/L); aspartate aminotransferase (AST), 141 U/L (reference range, 15–45 U/L); alanine aminotransferase (ALT), 73 U/L (reference range, 9–60 IU/L); gamma-glutamyl transpeptidase (GGT), 187 U/L (reference range, 10–60 U/L); alkaline phosphatase, 683 U/L (reference range, 45–125 U/L); creatinine (Cr), 95 μmol/L (reference range, 57–97 μmol/L); prothrombin time (PT), 22.6 s (reference range, 11–14 s); international normalized ratio (INR), 1.8 (reference range, 0.8–1.15); and whole blood ammonia, 33 μmol (reference range, 9–31 μmol/L). Serology revealed no infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), hepatitis G virus (HGV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), Hantaan virus, toxoplasmosis, Coxiella burnetii, or leptospirosis. There were no signs of metabolic disorders such as galactosemia, Wilson's disease, hemochromatosis or autoimmune disease (systemic lupus erythematosus), or intoxication (no history of alcohol or other toxins intake). Biliary obstruction was excluded after abdominal ultrasonography or CT. Then, the diagnosis of AIH complicated with FHF was established. The patient received comprehensive medical treatment after admission to the hospital, including general supportive treatment, energy and vitamin supplements, supplementation of blood products, such as washed red blood cells, albumin and plasma, and treatment of potential complications, all failed to improve his condition. Therefore, NBAL, alternating TPE with DPMAS was employed after obtaining written informed consent. Right femoral vein was catheterized as vascular access. The Prismaflex V8 blood purification device and indispensable accessories (Gambro) were used for TPE, and the plasma separator TPE2000 (Gambro) was applied. Blood pumping speed was 120 to 150 ml/min, the plasma separating speed was about 25 ml/min, and the plasma separation ratio was 30%. The amount of FFP in TPE was about 2400 ml per treatment, and the time for a single treatment was about 2 h. Prior to TPE, 25 mg promethazine hydrochloride was routinely administered via intramuscular injection to prevent plasma allergy. DPMAS was applied using the Multifiltrate CiCa® device (FMC; Bad Homburg). Briefly, the blood first flowed through the P2 plasma separator (FMC; Bad Homburg) after being pumped out of the body at a plasma separation speed of 25 to 30 ml/min, and the plasma then flowed sequentially through the ion exchange resin (BS330, Zhuhai Health Sails Biotechnology Co., Ltd.) and the neutral macroporous adsorption resin (HA330-II, Zhuhai Health Sails Biotechnology Co., Ltd) and was mixed with the blood cells and infused back into the patient, with a blood pumping speed of 120–150 ml/min during the treatment. The processed plasma volume for a single treatment by DPMAS was approximately 5 L for about 3 to 4 h. Treatment was not able to proceed without anticoagulant due to hypercoagulability of the whole body. Low doses of unfractionated heparin (UFH; initial dose 4 mg and then maintained by 1 mg/h) neutralized with protamine

(1.25 mg/h) were used for anticoagulation. Bilirubin (total bilirubin TBIL, direct bilirubin DBIL, indirect bilirubin IBIL, and δ bilirubin δBIL) was examined both pre- and post-treatment. Ammonia and liver enzyme were also recorded periodically. Data were described using means with corresponding standard deviations. The paired t test was used to compare means of percentage changes between pre- and post-runs. Since this was an exploratory analysis, p values of <0.05 were considered to be statistically significant in a descriptive manner. Analysis was performed using GraphPad Prism v9.0 for Mac OSX (GraphPad Software). The results showed that there was no significant difference between TPE and DPMAS for removing TBIL, DBIL, IBIL, and δBIL ($p > 0.05$, Figure 1), but subgroup analysis revealed that DPMAS seemed to be superior to TPE for removing TBIL and IBIL ($p < 0.05$, Figure 1A,C). Both DPMAS and TPE can decrease DBIL considerably ($p < 0.05$, Figure 1B). Ammonia level is paralleled to TBIL level (Figure 2). No obvious adverse events were observed. The patient sustained for about one month using this treatment modality. However, it was a pity that the patient died one month later without receiving timely liver transplantation.

3 | DISCUSSION

More and more attention has been drawn to FHF due to the poor prognosis arising from rapid onset and progression.[13] Except liver transplantation, there are no effect drugs for FHF. To address the problem, artificial liver support system (ALSS) is conceived in liver failure for temporary and partial replacement of liver function, which can bridge the critical waiting period for liver transplantation or liver function recovery. Among ALSS, NBAL is predominantly used in clinical practice, probably due to the rapid development of biological materials. There are three main types of NBAL, including dialysis, adsorption, and plasma exchange.

As one classical type of NBAL, TPE has been widely used in FHF in that it can reduce liver injury and systemic toxic reactions by clearing inflammatory mediators and harmful substances from blood, replenish the essential protein (albumin, clotting factors) and regulate immune cell activity. Specifically, TPE was shown to reduce levels of circulating inflammatory cytokines (TNF-α, IL-8, etc.), improve hemodynamics, coagulopathy, and transplant-free survival in FHF.[14–17] In addition, TPE modulates adaptive immunity in ALF through the reduction of soluble B7 molecules (particularly sCD86), which are produced by injured hepatocytes and can increase the expression of cytotoxic T-lymphocyte-associated protein 4 on CD4+ T cells, resulting in impaired antimicrobial responses and increased susceptibility to infections.[18] While encouraging, head-to-head comparisons between the studies supporting these findings have been challenging because of the broad variation in treatment protocols such as volume of exchange, treatment frequency, and duration of therapy varying between studies. The only RCT associated with TPE was about high-volume TPE (HV-TPE). The result demonstrated that compared with standard medical treatment (SMT), patient received HV-TPE manifested significantly improved mean arterial blood pressure (MAP), reduction in vasopressor requirement, stable renal function (no need for renal replacement), and improvement in transplant-free survival.[15] However, that

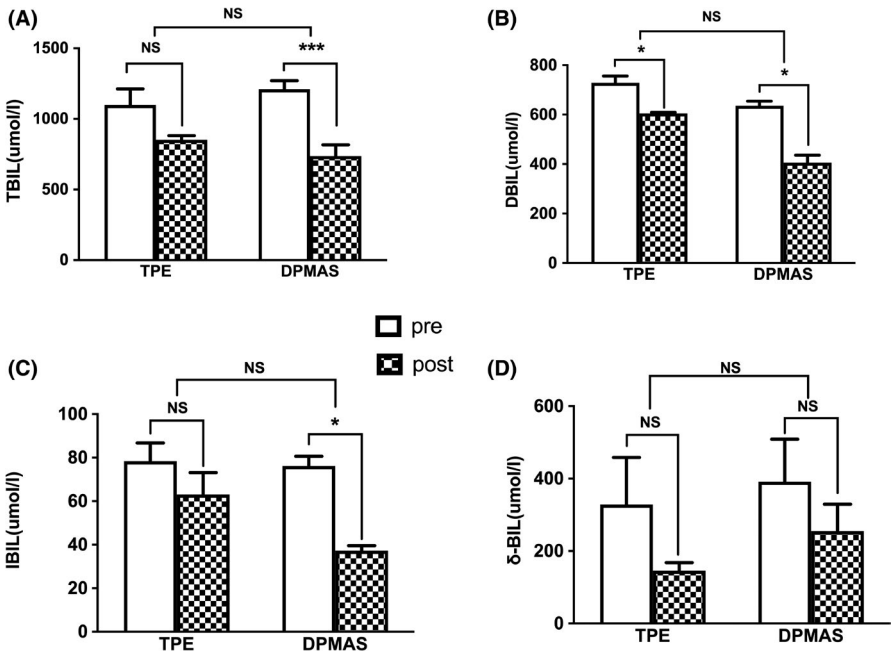

FIGURE 1 Comparison of bilirubin removal by therapeutic plasma exchange (TPE) and double plasma molecular adsorption system (DPMAS) (*$p < 0.05$, ***$p < 0.01$). A, total bilirubin, TBIL; B, direct bilirubin, DBIL; C, indirect bilirubin, IBIL; D, δ-bilirubin, δBIL

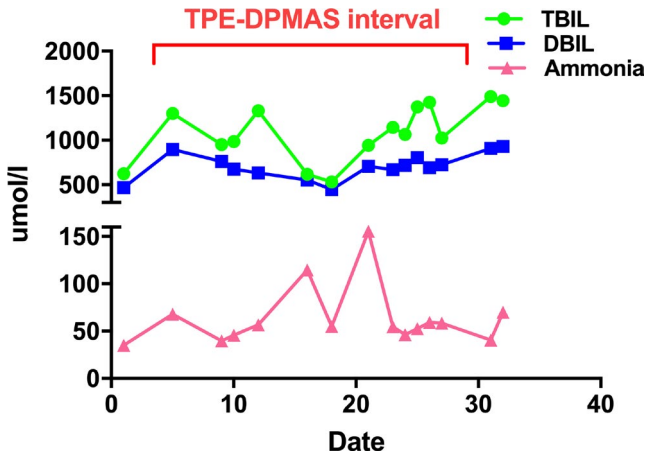

FIGURE 2 Trend of bilirubin and blood ammonia during the whole treatment period

is not the case of standard volume TPE.[16] TPE is limited due to inadequate plasma supply and increase in the risk of blood-borne communicated diseases, allergic reaction, hyponatremia, etc.

Adsorption is another type of NBAL. The DPMAS adds a broad-spectrum adsorption column (HA330-II) to bilirubin adsorption column (BS330). It offers an efficient method to fully and constantly remove the medium- and macro-molecules and protein-bound toxins, while specifically eliminating the bilirubin, without need to supplement plasma or replacement solution during treatment. DPMAS successfully decreases the level of bilirubin, ammonia, bile acid in acute-on-chronic liver failure (ACLF),[11,12,19] but there are few reports on FHF.

Given limited role and different principle and function of a single type, combination treatment modality is employed more frequently, like plasma exchange plus plasma adsorption plus continuous venous-venous hemodialysis/hemodiafiltration (PE+PA+CVVH), PE+CVVHDF, or PA+CVVH,[20] in order to use their respective advantages to complement each other and make the best of different methods. DPMAS in combination with TPE is a successful example, no matter of the combination order (sequential) or dosage (half volume), which was demonstrated more efficient than each being used separately to treat ACLF patients.[19,21,22]

In this case, DPMAS and TPE were performed alternatively every other day for more than one month, benefiting from the adequate supply of FFA. The consideration was mainly based on the following two points: (1) decreased the duration of treatment per session and enough time left for the patient to rest; (2) the replacement fluid of TPE is FFP all the time, so after TPE, there was sufficient time for the adsorption and redistribution of "precious fluid" to help the liver regenerate and recover. Treatment was not able to proceed without anticoagulant due to hypercoagulability of the whole body. So low doses of UFH (initial dose 4mg and then maintained by 1 mg/h) neutralized with protamine (1.25 mg/h) were used for anticoagulation.

We for the first time reported the alternative TPE with DPMAS in FHF and meantime compared the clearance efficiency in bilirubin. It was proved that bilirubin removal was largely identical with both procedures. But subgroup analysis indicated that DPMAS seemed to be superior to TPE for removing TBIL and IBIL, which was contradictory to the previous report.[11] Perhaps, the duration time of DPMAS was longer enough for bilirubin to bind adsorbent until reaching saturation. Given the difficulty of ammonia testing (very short time to upload in machine), the change of ammonia level during treatment was not compared between the two groups. The plot showed that ammonia level was paralleled to that of TBIL. During the whole treatment period, the patient's condition was once stable or even better. But due to no recovery of liver cells' function and lack of timely donor liver, the wastes accumulated faster than the removal and replenishment were not enough to offset consumption, and his condition finally deteriorated at the end of the course. In the end, the patient sustained more about one month by this technique without any obvious adverse events.

4 | CONCLUSION

Alternating TPE with DPMAS can rapidly remove bilirubin and ammonia and supplement the essential substance from the blood, which could be used as an effective transitional treatment for ALF. With TPE and DPMAS performed alternatively, homeostasis could be maintained for a longer period. However, more clinical trials are needed to verify the long-term efficacy in the future.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

Yan Lei and Zhihua Zheng contributed to the conception of the study. Xumei Zhang and Xiaohua Wang performed the treatment. Yu Zhang and Yuk Ming Chan performed data collecting. Yan Lei and Yuling Liang performed the data analyses and wrote the manuscript. Chun Tang helped revise the manuscript. Zhihua Zheng helped perform the analysis with constructive discussions.

ETHICAL APPROVAL

Obtained.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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