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Effectiveness of High-Volume Therapeutic Plasma Exchange for Acute and Acute-on-Chronic Liver Failure in Korean Pediatric Patients

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Liver transplantation (LT) is the only curative treatment for acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). In high-volume therapeutic plasma exchange (HV-TPE), extracorporeal liver support filters accumulate toxins and improve the coagulation factor by replacing them. In this study, we aimed to evaluate the effectiveness of HV-TPE in pediatric patients with ALF and ACLF.
Methods: We reviewed the records of children waiting for LT at Severance Hospital who underwent HV-TPE between 2017 and 2021. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin (TB and DB), gamma-glutamyl transferase (GGT), ammonia, and coagulation parameter-international normalized ratio (INR) were all measured before and after HV-TPE to analyze the liver function. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Co., Armonk, NY, USA).
Results: Nine patients underwent HV-TPE with standard medical therapy while waiting for LT. One had neonatal hemochromatosis, four had biliary atresia, and the other four had ALF of unknown etiology. Significant decreases in AST, ALT, TB, DB, GGT, and INR were noted after performing HV-TPE (930.38–331.75 IU/L, 282.62–63.00 IU/L, 11.75–5.59 mg/dL, 8.10–3.66 mg/dL, 205.62–51.75 IU/L, and 3.57–1.50, respectively, $p<0.05$). All patients underwent LT, and two expired due to acute complications.
Conclusion: HV-TPE could remove accumulated toxins and improve coagulation. Therefore, we conclude that HV-TPE can be regarded as a representative bridging therapy before LT.

Keywords: Acute liver failure; Acute-on-chronic liver failure; Therapeutic plasma exchange; Children; Liver transplantation

INTRODUCTION

Acute liver failure (ALF) is a rare disease with a very high mortality rate even with appropriate treatment [1,2]. There are two categories of ALF in children: ALF, which occurs without any underlying disease; and acute-on-chronic liver failure (ACLF), which shows acute exacerbation in children with underlying diseases [3]. Both are rare, but when they occur,

synthetic and metabolic functions of the liver deteriorate, and toxins and immune substances accumulate in the body, which can lead to multiorgan failure [3,4].

Standard medical therapy (SMT) is commonly used in patients who develop ALF and ACLF [3,4]. The purpose of SMT is to treat ALF and ACLF by providing sufficient time for liver regeneration. However, in some cases, SMT has limited effectiveness, and liver transplantation (LT) is eventually required to treat the patient. Among the extracorporeal liver support used in adults, high-volume therapeutic plasma exchange (HV-TPE) has proven to be effective for LT-free survival [5]. In 2019, the American Society for Apheresis recommended HV-TPE as category 1 (accepted as first-line therapy) and grade 1A (strong recommendation, high-quality evidence) in patients with ALF [6]. TPE is also recommended in the European ALF treatment guidelines [3]. Although the use of HV-TPE in adults is recommended, there are limited proven examples of its efficacy in children. Several studies have reported that HV-TPE is effective in children who develop ALF due to Wilson's disease [7,8].

Since 2017, our institution has been conducting HV-TPE on children waiting for LT using a prismaflex machine and the TPE-2000 kit. Before LT, we applied HV-TPE to stabilize the condition of the patients. In this study, we aimed to evaluate the effectiveness of HV-TPE in pediatric patients with ALF and ACLF. To the best of our knowledge, this is the first study to evaluate the efficacy of HV-TPE in Korean children with ALF or ACLF.

MATERIALS AND METHODS

We reviewed the records of children waiting for LT at Severance Hospital who underwent HV-TPE between January 2017 and August 2021. The timing of LT was determined according to King's College Criteria (KCC) for non-acetaminophen-related ALF and pediatric end-stage liver disease (PELD) score [9,10]. All patients underwent SMT, which includes maintaining vital signs, appropriate volume status, and the balance of electrolytes and glucose, and managing intracranial pressure (ICP) in cases of hepatic encephalopathy (HE). Lactulose was used to control hyperammonemia and mannitol was used for ICP management. Renal replacement treatment and ventilation were not administered to all patients and were used only when necessary. Laboratory data was collected for the analysis of liver function tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin (TB and DB), gamma-glutamyl transferase (GGT), ammonia, and coagulation parameter-international normalized ratio (INR), before and after HV-TPE. For statistical analysis, the Wilcoxon signed-rank test and Mann–Whitney U-test were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Co., Armonk, NY, USA). The statistical significance was set at $p<0.05$. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Severance Children's Hospital (IRB number: 4-2022-0233). The requirement for informed consent was waived because of the retrospective nature of the study.

HV-TPE procedure

The HV-TPE procedure was performed using a prismaflex machine (Gambro, Lund, Sweden) and a TPE-2000 kit (GAMBRO Industries, Meyzieu, France). The patient's plasma was drawn using a TPE kit membrane to remove toxins and immune substances, and fresh frozen plasma (FFP) was infused simultaneously to replace the removed plasma. The patient's total body volume (TBV) and plasma volume (PV) were calculated using the following formulas.

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TBV=weight (kg)×80 mL/kg
PV=TBV×(1.0−hematocrit [%])

HV-TPE is the exchange of three times the patient's estimated PV through TPE. The blood flow rate was set to 2 mL/kg/min. The replacement fluid rate can be adjusted in 50 mL/h increments, and it was adjusted based on each patient's clinical status and hemodynamic stability. Nafamostat mesylate was infused as an anticoagulant at 0.1 mg/kg/h. When HV-TPE is applied, vital sign instability may occur because of blood plasma alteration and blood loss from the prismaflex machine. For body volume adjustments, red blood cell transfusion was performed simultaneously when the machine started. Before and after TPE, blood tests were performed to check for improvement in liver function and TPE complications like thrombocytopenia and hypocalcemia [11].

RESULTS

General characteristics

Nine patients underwent TPE before LT between 2017 and 2021. Four (44.4%) patients had ALF and five (55.5%) patients had ACLF. Among the patients with ACLF, four (44.4%) had biliary atresia and one (11.1%) had neonatal hemochromatosis. The average age at HV-TPE was 23.7±27.6 months, and the median age was 15 months. The PELD score before HV-TPE was reduced from 30.17±11.96 to 7.87±9.71 after HV-TPE. Although there was a marked decrease in the PELD score after TPE, LT was determined by KCC, PELD score, and general condition before HV-TPE. Five (55.5%) patients received continuous renal replacement therapy (CRRT) in continuous venovenous hemodiafiltration mode and ventilation with intubation. Four (44.4%) patients were diagnosed with grade-1 HE and two (22.2%) with grade-2 HE. Electroencephalography (EEG) showed that one (11.1%) patient had a stuporous mentality and a grossly abnormal slowing down, which was confirmed as grade-3 HE. In two (25%) patients, the mental status could not be reviewed due to sedation for central line insertion before the liver condition worsened (**Table 1**). One of the patients who failed to check their mental status was classified as grade 2 due to the generalized abnormal slow wave on EEG and the other was estimated to be grade 3 due to diffuse slow waves on EEG. Two patients died of acute complications after LT.

Pre- and post-HV-TPE parameters

Table 2 shows the blood test results related to liver function and the possible complications before and after TPE. AST, ALT, TB, DB, INR, prothrombin time, and ammonia levels decreased after TPE (**Table 2** and **Fig. 1**). Except for ammonia, the decrease in the other parameters was statistically significant. In the case of thrombocytopenia and hypocalcemia, which are typical complications that may occur during TPE, a mild decrease in platelet count was observed in this study, but the difference was not statistically significant. In the case of calcium, the results showed an increase, and there were no significant complications.

Repetitive effects of HV-TPE

Of the nine patients, four of the five with ACLF and two of the four with ALF underwent at least two HV-TPE treatments. **Table 3** compares the blood test results showing liver function before the first and second HV-TPE procedures. As shown in the table, all the parameters decreased. Decreases in TB, DB, and INR were statistically significant. **Table 4** also compares the laboratory test results after the first and second HV-TPE. The overall values of AST, ALT,

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Table 1. Basal characteristics

Clinical parameters	Total (n=9)	Male (n=3)	Female (n=6)
Diagnosis			
Biliary atresia	4 (44.4)	0	4 (44.4)
Acute liver failure (unknown)	4 (44.4)	3 (33.3)	1 (11.1)
Neonatal hemochromatosis	1 (11.1)	0	1 (11.1)
TPE (mo)			
Average	23.7±27.6	38.3±45.9	16.4±13.6
Median	15	16.9	13.3
PELD score			
Pre-TPE	30.17±11.96	29.7±1.38	29±15.53
Post-TPE	7.87±9.71	2.4±2.27	9.5±11.2
CRRT			
Application	5 (55.5)	2 (22.2)	3 (33.3)
Non-application	4 (44.4)	1 (11.1)	3 (33.3)
Ventilator			
Apply	6 (66.6)	3 (33.3)	3 (33.3)
Not apply	3 (33.3)	0	3 (33.3)
Hepatic encephalopathy			
Cannot be checked	2 (22.2)	0	2 (22.2)
Grade 1	4 (44.4)	1 (11.1)	3 (33.3)
Grade 2	2 (22.2)	2 (22.2)	0
Grade 3	1 (11.1)	0	1 (11.1)

Values are presented as number (%) or mean±standard deviation.
TPE: therapeutic plasma exchange, PELD: pediatric end-stage liver disease, CRRT: continuous renal replacement therapy.

Table 2. Biochemical parameters before and after HV-TPE treatment

Laboratory factors	Pre-TPE	Post-TPE	*p*-value
AST (IU/L)	930.38±1,566.68	331.75±656.99	0.025*
ALT (IU/L)	282.62±338.61	63±41.24	0.017*
TB (mg/dL)	11.75±5.27	5.59±5.78	0.012*
DB (mg/dL)	8.1±3.81	3.66±4.59	0.012*
GGT (IU/L)	205.62±274.13	51.75±39.94	0.017*
Ammonia (μg/dL)	129.88±64.83	106.88±41.19	0.262
PT (sec)	41±23.20	17.3±5.69	0.012*
INR	3.57±2.13	1.50±0.57	0.012*
Platelet (/μL)	135,875±86,733.48	111,875±64,357.12	0.123
Calcium (mg/dL)	8.85±0.60	9.27±1.61	0.779

Values are presented as mean±standard deviation.
HV: high-volume, TPE: therapeutic plasma exchange, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TB: total bilirubin, DB: direct bilirubin, GGT: gamma-glutamyl transferase, PT: prothrombin time, INR: international normalized ratio.
p-values are calculated using the Wilcoxon singed rank test (*p-value<0.05).

TB, DB, GGT, and ammonia, excluding the INR, decreased. However, this decrease was not statistically significant. Additionally, the difference between the group that had a single HV-TPE and the group that had more than one HV-TPE before LT was compared. As LT is determined by the KCC and PELD scores, TB, INR, and albumin were compared. **Table 5** shows the initial INR, TB, and albumin differences between the trial group with a single HV-TPE procedure and that with multiple applications. The INR, TB, and albumin levels of the two groups were not statistically significant, with *p*-values of 1.0, 0.38, and 0.26, respectively.

DISCUSSION

According to numerous guidelines and published papers, in adults, it is helpful to use extracorporeal liver supports, such as molecular adsorbent recycling systems or TPE, when

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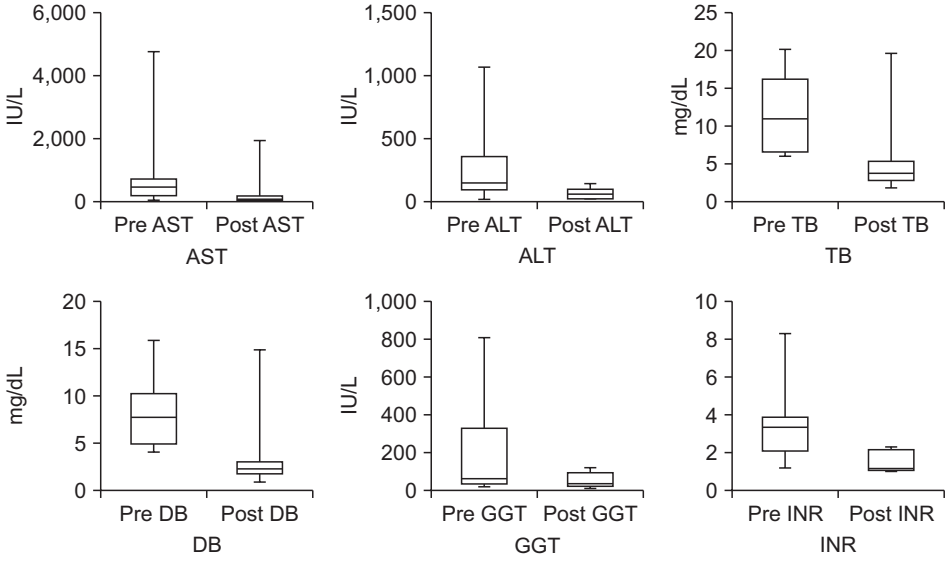

Fig. 1. Biochemical parameters before and after HV-TPE treatment. AST, ALT, TB, DB, GGT, and INR levels decreased after HV-TPE.
HV: high-volume, TPE: therapeutic plasma exchange, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TB: total bilirubin, DB: direct bilirubin, GGT: gamma-glutamyl transferase, INR: international normalized ratio.

Table 3. Comparison of liver function parameters before the first HV-TPE trial with those before the second trial

Laboratory factors	1st pre-TPE	2nd pre-TPE	*p*-value
AST (IU/L)	1,023.33±1,840.54	926±1,798.44	0.075
ALT (IU/L)	288.5±395.1	132.66±111.70	0.116
TB (mg/dL)	11.95±5.29	8.66±2.92	0.046*
DB (mg/dL)	8.81±4.04	5.98±2.30	0.043*
GGT (IU/L)	212.16±309.05	59±72.82	0.080
Ammonia (μg/dL)	104.66±48.55	99±53.98	0.893
INR	3.93±2.36	2.10±0.88	0.028*

Values are presented as mean±standard deviation.
HV: high-volume, TPE: therapeutic plasma exchange, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TB: total bilirubin, DB: direct bilirubin, GGT: gamma-glutamyl transferase, INR: international normalized ratio.
p-values are calculated using the Wilcoxon singed rank test (*p-value<0.05).

Table 4. Comparison of liver function parameters after the first HV-TPE trial with those after the second trial

Laboratory factors	1st pose-TPE	2nd post-TPE	*p*-value
AST (IU/L)	477.4±827.39	387±775.37	0.416
ALT (IU/L)	78.4±44.95	48.83±36.91	0.225
TB (mg/dL)	6.36±6.55	4.05±2.41	0.173
DB (mg/dL)	4.36±5.18	2.7±1.74	0.176
GGT (IU/L)	67.2±43.09	21.66±4.72	0.285
Ammonia (μg/dL)	100.2±20.29	125.33±63.61	0.593
INR	1.50±0.55	1.19±1.02	0.715

Values are presented as mean±standard deviation.
HV: high-volume, TPE: therapeutic plasma exchange, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TB: total bilirubin, DB: direct bilirubin, GGT: gamma-glutamyl transferase, INR: international normalized ratio.
p-values are calculated using the Wilcoxon singed rank test (*p-value<0.05).

the liver condition rapidly deteriorates, and it helps to increase LT-free survival [5,6]. To the best of our knowledge, this is the first study to evaluate the efficacy of HV-TPE in Korean children with ALF or ACLF. In our institution, there are limitations when only SMT is used on patients with ALF and ACLF; accordingly, LT is considered a curative treatment. Owing

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Table 5. Differences in INR, TB, and albumin levels between the first HV-TPE and multiple rounds of HV-TPE

HV-TPE application	Once	More than twice	*p*-value
INR	5.65±5.52	3.93±2.37	1.0
TB (mg/dL)	8.6±6.78	11.95±5.29	0.38
Albumin (g/dL)	3.5±0.40	3.03±0.66	0.26

Values are presented as mean±standard deviation.
INR: international normalized ratio, TB: total bilirubin, HV-TPE: high-volume therapeutic plasma exchange.
p-values are calculated using the Mann–Whitney U-test (p-value<0.05).

to these limitations, we attempted to determine whether HV-TPE is effective in pediatric patients. In a comparison of toxic substances, liver function tests, and coagulatory profiles before and after the first HV-TPE application, a significant decrease was observed in the values of AST, ALT, TB, DB, GGT, and INR. Based on these results, we suggest that HV-TPE filters toxins from the body and improves coagulation factors to enhance the patient's condition and prepare for LT in a more stable state.

The most representative complications, such as thrombocytopenia and hypocalcemia, were not statistically significant in our cases [2]. In one study, 10% calcium gluconate was infused during TPE for proactive correction, with frequent arterial blood gas monitoring for ionized calcium [2]. Since hypocalcemia did not occur in our cases, it was sufficient to check the blood test results and replace calcium, if necessary. The platelet count showed an overall decrease after HV-TPE; however, this was not statistically significant. It is unclear whether such a decrease in platelet count is either due to ALF and ACLF or the implementation of HV-TPE.

It has been reported that HV-TPE is effective in reducing ammonia and is helpful for HE [11,12]. An overall decrease in ammonia level was observed in our cases, but the decrease was not statistically significant. This can be interpreted in two ways: First, the number of patients was too small to achieve statistical significance. Second, the TPE filter has a structure that is suitable for filtering medium-sized molecules. Ammonia is a small molecule that can pass through the membrane pores of TPE relatively easily compared to other types of molecules. Applying CRRT, which uses a filter with a membrane pore smaller than that of TPE, is more effective in removing ammonia. Five of the eight patients who had CRRT with HV-TPE had a drop in their overall levels of ammonia. In the case of HE, most patients were sedated for ventilator application, CRRT administration, or line insertion. The post-TPE HE status could not be identified.

To confirm the effects of repetitive HV-TPE, the blood test results before and after the first and second HV-TPE procedures were compared. The blood test showed an overall decrease in numbers, with a few showing statistical significance. When repetitive HV-TPE treatments were performed, there was no association between the number of treatments and post-trial blood test results, but the pre-trial test results improved. It can be inferred that the HV-TPE procedure does not affect the patient's liver function, but it plays a significant role in providing the time for liver regeneration when multiple HV-TPE treatments are performed. Moreover, we compared the initial INR value and TB and albumin levels (components of the PELD score and KCC) of the single-treatment TPE trial group with those of the two-treatment TPE trial group until LT was completed. There was no difference between these variables, which indicates that a simple blood test has limitations in predicting the time to LT.

A limitation of this study was the small sample size. The incidence of ALF and ACLF was low, resulting in statistical limitations. Further studies with larger sample sizes are required.

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Another limitation is the timing of the application. In the case of HV-TPE, there is no clear indication of its application. For example, in the case of LT, our institution uses the PELD score and KCC to determine whether to perform LT. However, there is no clear standard for the application of HV-TPE; therefore, it can be applied when TB elevation is observed, when organ failure progresses owing to ALF, or when HE progresses. At our institution, HV-TPE was administered to patients who required LT due to ALF or ACLF. A clear indication of the application of HV-TPE must be established to compare its effects. This is consistent with the findings of other studies that have shown that HV-TPE is used to increase the time for liver regeneration [13,14].

There are several difficulties associated with administering TPE to children. Most children receive a living-donor liver from their parents, due to which transplantation proceeds rapidly. Others require a hemocatheter for TPE, where line insertion becomes another hurdle in pediatric patients. At the onset of TPE, the patient's PV may be filtered simultaneously, resulting in temporary instability. Vital instability can be adjusted by using transfusions for volume supply and inotropic agents simultaneously with the initiation. As demonstrated in our study, the advantages of TPE include the removal of toxins and improved coagulation. In addition, since living-donor transplants require a donor examination before LT, TPE provides adequate time to perform such examinations. Considering these limitations and benefits, it will be helpful for patients to actively use TPE when necessary.

In the future, it will be necessary to collect and analyze more cases of TPE treatment in children. Accurate indications of how to apply TPE must be established to appropriately apply it to children, if necessary. In addition, to confirm the results of TPE application, research on the relationship between TPE usage and surgical performance, postoperative conditions, and survival is also needed. Also, research is needed to compare the effectiveness of HV-TPE in children with and without LT.

In conclusion, HV-TPE can remove accumulated toxins and improve coagulation. Therefore, we concluded that HV-TPE stabilizes the condition of the patient and can be regarded as a representative bridging therapy before LT.

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