J Chen, *et al.*
www.hepato-gastroenterology.org
DOI 10.5754/hge12025
2012; 59(119): Ahead of print.

Hepato-Gastroenterology

Liver, Original Open Access, Ahead of Print

# A Clinical Study on the Treatment of Severe Hepatitis by a Combined Artificial Liver

*Jiajia Chen, Jianrong Huang, Yuemei Chen, Yinfeng Lu and Lanjuan Li*

State Key Laboratory for Diagnosis and Treatment of Infectious Diseases,
The First Affiliated Hospital, School of Medicine, Zhejiang University, China

Corresponding author: Ass. Prof. Lanjuan Li, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310003, China; E-mail: ljli@zju.edu.cn

**KEY WORDS**: Severe hepatitis; Selective blood plasma exchange; Selective plasma perfusion/absorption.

## ABSTRACT

**Background/Aims**: To focus on determining efficacy and safety of the combined artificial liver in treating severe hepatitis. **Methodology:** Ten patients with acute and chronic severe hepatitis were chosen for this study. A total of 19 cases were treated with a combination of selective plasma absorption and selective plasma exchange and 1 was treated with plasma perfusion absorption. Clinical symptoms and physical signs were observed. In addition, the changes in biochemical markers, coagulation function, and aminogram before and after selective plasma perfusion absorption treatment were compared. **Results:** Ten patients were able to tolerate the treatment; 8 patients were cured or improved whereas 2 worsened. Statistically significant differences ($p<0.05$) were observed in the serum levels of total bilirubin, direct bilirubin, indirect bilirubin, alanine transaminase, aspartate transaminase, alkaline phosphatase, total bile acids, albumin and globulin before and after the selective perfusion absorption treatment. In contrast, no statistically significant differences ($p>0.05$) were observed in the serum concentrations of potassium, sodium, creatinine and urea nitrogen, as well as in prothrombin time, partial thromboplastin time and aminogram changes. **Conclusions:** The new perfusion absorber can markedly improve hepatic function without influencing the metabolism of micro-molecules and coagulation factors.

## INTRODUCTION

Artificial liver support system (ALSS) has been applied to treat severe hepatitis since the 1990s and has saved numerous patients by reducing metabolic toxins until more permanent treatments, like regeneration of liver cells, are developed (1). At present, the focus of ALSS studies is moving from the non-biological to the biological (2). Studies of non-biological artificial livers concentrate mostly on the optimized combination of various non-biological artificial liver support systems. This paper studied combined selective plasma absorption and selective plasma exchange, analyzed the changes in biochemical and clotting function and in the aminogram before and after selective plasma perfusion/absorption and examined the features of a new perfusion absorber and the efficacy and safety of this combination for artificial liver treatment.

## METHODOLOGY

### Choice of clinical cases

Ten patients with severe hepatitis were hospitalized at the First Affiliated Hospital of Zhejiang University Medical School in 2009. The patient group included nine males and one female with an average age of 38.9. They were diagnosed according to the criteria developed by National Epidemic Disease and Parasitic Disease Conference in 2000 (Xi'an, China). Three cases were triggered by medicine, six were triggered by hepatitis B virus and one was triggered by hepatitis E virus. They were classified into clinical types: four early-phase, five middle-phase and one late-phase. Total bilirubin in one case was >684μmol/L, four cases were 513-684μmol/L, three cases were 342-513μmol/L, one case was 171-342μmol/L and one case was <171μmol/L. All ten patients reported different degrees of debilitation, including poor digestion, nausea and abdominal distension and one patient had complicated hepatic encephalopathy.

### Treatment plan

Hospitalized patients with severe hepatitis received the regular treatment options, including hepatocyte growth factor, compound glycyrrhizinate gel, Kuhuang, albumin

and plasma, as well as the treatment protocol described here. Patients were treated with combined selective plasma perfusion/absorption and selective plasma exchange or just pure selective plasma perfusion/absorption. Nine patients were treated by the combined therapy and one patient was treated with plasma perfusion absorption only. Clinical symptoms and change of physical signs were observed during the treatment.

### Instruments

The selective plasma separator used was an EC-40W (Asahi Kasei) and the perfusion absorber used was a HA-330+ new absorber (Zhuhai Jianfen Biotechnical).

### Method of inspection

Venous blood was collected from the forearms of patients before and after the selective plasma perfusion/absorption treatment to measure serum free amino acids, serum biochemistry test, and clotting functional indices on a Hitachi L-8800 amino acid automatic analyzer, an Abbott's Aeroset full-automatic analyzer and a Sysmex CA700 full-automatic clotting analyzer.

### Statistical methods

Statistical analyses were performed using the SPSS 16.0 for Windows statistics package.

## RESULTS

### Clinical outcomes

After treatment by combinational artificial liver, eight patients demonstrated both physical and psychological improvement, including improved digestion, alleviation of abdominal distension and reduced jaundice. Three patients experienced a rebound of serum total bilirubin that ranged from 18.2-93.5% (median 41.2%). Among the ten patients, two were cured, six improved and two worsened, representing an 80% improvement (8/10). One patient had acute liver failure and only received selective plasma perfusion/absorption because of the defect of venous plasma supplement. The

patient eventually regained liver function. Detailed changes in serum aminogram, serum biochemistry and clotting function before and after treatment with selective plasma perfusion/absorption were presented in **Tables 1** and **2.**

**Safety**

Patient receiving combined selective plasma perfusion/absorption or selective plasma exchange did not develop complication like rash or hypotension during the period of absorption treatment. Regular blood tests showed no difference in white blood cell or platelet count before and after the selective plasma perfusion/absorption. Hemoglobin was reduced from 107.89±13.94g/L before the treatment to 103.58±16.03g/L after the treatment and red blood cells were reduced from $3.67\pm1.00\times10^{9}$/L to $3.57\pm1.04\times10^{9}$/L ($p<0.05$). During the entire treatment, four cases developed a rash accompanied by itching but symptoms were alleviated by proper treatment. All nine patients tolerated the combined artificial liver treatment and no patient withdrew due to intolerable complications.

**DISCUSSION**

Artificial liver support (ALSS) through combined plasma replacement, perfusion and absorption or blood dialysis and filtration, temporarily improved liver function, stabilized many indices of liver function and ameliorated the effects of hepatic necrosis by allowing regeneration of liver cells. Artificial liver support involves different methods, depending on the patients' condition and the etiology of liver disease. Non-biological artificial liver support is still the main method of liver treatment of severe hepatitis at present. The combination of a new perfusion/absorber and selective plasma exchange has not been assessed in large scale clinical trials.

During treatment, we assessed changes in serum amino acids, blood biochemistry and clotting function before and after combined plasma perfusion/absorption and exchange. We found that total bilirubin, direct bilirubin, indirect bilirubin, glutamic-pyruvic transaminase, aspartate transaminase, alkaline phosphatase and total bile acid were significantly reduced ($p<0.001$) by 32.19±7.12%, 24.07±15.83%,

44.90±24.40%, 10.64±11.60%,17.82±12.30%, 3.5±7.7% and 17.53±21.37%. The reduction in albumin and globulin were also statistically significant ($p$<0.001) while changes in prothrombin, electrolytes, creatinine and urea nitrogen were not statistically different after the treatment ($p$>0.05). Meanwhile, we observed no significant changes in serum amino acids after the selective plasma perfusion/absorption. Before the treatment, aromatic amino acids (including methionine, phenylalanine and tyrosine) were higher than normal as is usually observed in severe hepatitis, but branch chain amino acids/aromatic amino acids (BCAA/AAA) were reduced to 0.3913±0.13716. The changes in total serum amino acids and percentage of branched chain amino acids were not statistically different after the selective plasma perfusion/absorption ($p$>0.05). According to our results, the perfusion/absorber could improve liver function but did not cause loss of blood coagulation factors, influence the metabolism of small-molecules or alter the aminogram.

The efficacy of treating liver failure with pure plasma exchange or pure selective plasma exchange has been demonstrated (3). Application of the combination of plasma exchange and absorption and blood dialysis and filtration (non-biological artificial liver) to treat chronic severe hepatitis was more effective than pure plasma exchange in improving hepatic encephalopathy, restoring electrolyte balance and increasing short-term survival ratio (4). The combined selective plasma perfusion/absorption described in this paper not only complements the selective plasma exchange by improving liver function and enhancing toxin metabolism but also by saving limited plasma resources. This study reduced the one-time use of plasma from 3500mL to 1500mL without a drop in clinical efficacy. Therefore, this combined treatment shows promise for treatment of acute or chronic liver failure triggered by hepatitis or other liver diseases.

## ACKNOWLEDGMENTS

The research and publication were funded by the Chinese High Tech Research & Development (863) Program (No. 2011AA020104), Science Fund for Creative

Research Groups of the National Natural Science Foundation of China (No. 81121002) and the Technology Group Project for Infectious Disease Control of Zhejiang Province (No. 2009R50041).

## REFERENCES


1. **LJ Li, Q Yang, JR Huang, et al.:** Effect of artificial liver support system on patients with severe viral hepatitis: A study of four hundred cases. World J Gastroenterol 2004; 10(20):2984-2988.
2. **Pless G:** Artificial and bio-artificial liver support. Organogenesis 2007; 3(1):20-24.
3. **Li LJ, Liu XL, Xu XW, et al.:** Comparison of plasma exchange with different membrane pore sizes in the treatment of severe viral hepatitis. Ther Apher Dial 2005; 9(5):396-401.
4. **Jin J, Ye WJ, Yu HY, et al.:** Combined slower plasma exchange and continuous veno-venous hemofiltration with a parallel circuit in the treatment of chronic severe viral hepatitis B patients. Zhonghua Gan Zang Bing Za Zhi 2009; 17(2):95-98.

**TABLE 1.** Changes in the serum aminogram before and after treatment with selective plasma perfusion/absorption (μmol/ L, $x \pm s$).

| Aminogram | Pre-treatment | Post-treatment |
|---|---|---|
| ASP | 54.59±24.69 | 53.22±41.74 |
| THR | 579.24±295.95 | 692.15±421.60 |
| SER | 288.81±68.59 | 297.53±85.81 |
| GLU | 491.08±200.34 | 460.87±260.66 |
| GLY | 365.99±267.97 | 360.96±254.10 |
| ALA | 660.52±219.93 | 640.93±154.46 |
| CYS | 267.26±309.83 | 318.40±364.28 |
| VAL | 242.59±112.32 | 223.14±90.50 |
| MET | 331.57±356.95 | 323.52±298.26 |
| ILE | 94.45±43.81 | 110.67±68.01 |
| LEU | 148.55±73.79 | 128.12±47.64 |
| TYR | 185.50±93.43 | 184.52±71.57 |
| PHE | 178.61±46.81 | 186.65±63.30 |
| LYS | 358.12±187.37 | 351.98±154.96 |
| $NH_3$ | 601.80±284.64 | 582.67±164.24 |
| HIS | 230.11±186.32 | 234.90±204.41 |
| ARG | 133.86±65.40 | 147.26±67.30 |
| PRO | 269.7±53.76 | 281.17±74.74 |
| BCAA/AAA | 0.39±0.14 | 0.39±0.12 |

ASP: Aspartic Acid; THR: Threonine; SER: Serine; GLU: Glutamic Acid; GLY: Glycine; ALA: Alanine; CYS: Cysteine; VAL: Valine; MET: Methionine; ILE: Isoleucine; LEU: Leucine; TYR: Threonine; PHE: Phenylalanine; LYS: Lysine; HIS: Histidine; ARG: Arginine; PRO: Proline; BCAA/AAA: Branched chain amino acid/ Aromatic amino acid.

**TABLE 2.** Changes in serum biochemistry and clotting function before and after treating severe hepatitis with selective plasma perfusion/absorption.

| | **Pre-treatment** | **Post-treatment** | ***p* value** |
|---|---|---|---|
| ALB (g/L) | 33.54±3.22 | 28.45±1.61 | 0.000 |
| TBil (μmol/L) | 423.42±202.10 | 284.53±134.32 | 0.000 |
| DBil (μmol/L) | 265.11±120.49 | 205.53±105.73 | 0.000 |
| TBA (μmol/L) | 206.72±84.09 | 163.00±62.88 | 0.001 |
| ALT (U/L) | 176.42±280.11 | 153.79±254.59 | 0..033 |
| AST (U/L) | 118.84±82.19 | 93.79±59.79 | 0.005 |
| AKP (U/L) | 117.42±4.57 | 112.68±33.06 | 0.030 |
| APTT (S) | 50.58± 12.68 | 87.50±47.45 | NS |
| PT (S) | 17.80±8.84 | 23.56±16.69 | NS |
| $K^+$ (mmol/L) | 3.96±0.39 | 4.03±0.46 | NS |
| $Na^+$ (mmol/L) | 131.65±7.36 | 132.12±7.72 | NS |
| Cr (μmol/L) | 57.25±12.15 | 60.75±17.41 | NS |
| Bun (mmol/L) | 4.77±1.65 | 4.73±1.75 | NS |

ALB: Albumin; TBil: Total Bilirubin; DBil: Direct Bilirubin; TBA: Total Bile Acid; ALT: Aminotransferase; AST: Aspartate Aminotransferase; AKP: Alkaline Phosphatase; APTT: Activated Partial Thromboplastin Time; PT: Prothrombin Time; Cr: Creatinine; Bun: Urea Nitrogen.