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• ORIGINAL RESEARCH •

TECA hybrid artificial liver support system in treatment of acute liver failure

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Abstract

AIM: **To assess the efficacy and safety of TECA type hybrid artificial liver support system (TECA-HALSS) in providing liver function of detoxification, metabolism and physiology by treating the patients with acute liver failure (ALF).**

METHODS: **The porcine liver cells (1-2)×10¹⁰ were separate d from the Chinese small swine and cultured in the bioreactor of TECA-BALSS at 37.0℃ and circulated through the outer space of the hollow fiber tubes in BALSS. The six liver failure patients with various degree of hepatic coma were treated by TECA-HALSS and with conventional medicines. The venous plasma of the patients was separated by a plasma separator and treated by charcoal adsorbent or plasma exchange. The plasma circulated through the inner space of the hollow fiber tubes of BALSS and mixed with the patients' blood cells and flew back to their blood circulation. Some small molecular weight substances were exchanged between the plasma and porcine liver cells. Each treatment lasted 6.0-7.0 h. Physiological and biochemical parameters were measured before, during and after t he treatment.**

RESULTS: **The average of porcine liver cells was (1.0-3.0) ×10¹⁰ obtained from each swine liver using our modified enzymatic digestion method. The survival rate of the cells was 85%-93% by trypan blue stain and AO/PI fluorescent stain. After cultured in TECA-BALSS bioreactor for 6 h, the survival rate of cells still remained 70%-85%. At the end of TECA-HALSS treatment, the levels of plasma NH_3, ALT, TB and DB were significantly decreased. The patients who were in the state of drowsiness or coma before the treatment improved their appetite significantly and regained consciousness, some patients resumed light physical work on a short period after the treatment. One to two days after the treatment, the ratio of PTA increased warkedly. During the treatment, the heart rates, blood pressure, respiration condition and serum electrolytes (K^+, Na^+ and Cl^-) were stable without thrombosis and bleeding in all the six patients.**

CONCLUSION: **TECA-HALSS treatment could be a rapid, safe and efficacious method to provide temporary liver support for patients with ALF.**

Subject headings liver, artificial; liver failure; acute/therapy

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INTRODUCTION

Liver diseases are common in China[1-8]. The treatment for acute liver failure (ALF) is still a focus of research[9-15]. Some clinical reports have shown that non-biological-artificial liver support system with charcoal adsorbent or plasma exchange could improve the rehabilitation process in the patients with acute and chronic liver failure[16-25]. Our previous experiments have demonstrated that as a temporary alternative treatment, TECA type bioartificial liver support system (TECA-BALSS) using the swine liver cells was safe and effective in treating the ALF dogs induced by acetaminophen, with the injured liver cells regenerated and repaired, and a long-term survival[26-30]. In order to reduce the damage to the swine liver cells caused by the toxic substances in the ALF patients' blood and improve the efficacy of the treatment, we treated 6 patients with acute and chronic liver failure by our newly developed TECA type hybrid artificial liver support system (TECA-HALSS) using swine liver cells combined with charcoal adsorbent or plasma exchange.

MATERIALS AND METHODS

TECA-BALSS

The swines were purchased from the small swine breeding laboratory of Beijing Agricultural University. The porcine liver cells were separated by the enzyme method from Chinese experimental small swine and the survival rate of the cells was determined by trypan blue stain and AO/PI fluorescent stain. Porcine liver cells (1-2)×10¹⁰ were cultured in the T ECA-BALSS bioreactor at 37.0℃ and circulated through the outer space of the hollow fiber tubes in BALSS[31-32]. One of the femoral veins or subclavian veins of the patient was cut and a tube was inserted to establish the blood circulation pathway. The venous plasma of the patient was separated by a plasma separator and through the inner space of the hollow fiber tubes of BALSS and mixed with the patient's blood cells and flew back to their circulation.

Non-bioartificial liver support system

The plasma was treated by carbon absorption with Gambro Adsorda 300C and mixed with the patient's blood cells and flew back to their venous sys tem for 2-3 h in cases 1, 2 and 3. The patient's plasma was separated and exchanged for 2 to 3 L by PLASAUTO-IQ Plasma Exchanger (Japan) in cases 4, 5 and 6[33,34]. The heparin was administered to all the patients for anticoagulation.

TECA-HALSS

After the treatment with the non-bioartificial liver support system, the

patient's plasma was circulated through the inner space of the hollow fiber tubes in TECA-BALSS for 4-5 h.

Examination indexes

Before, during and after the treatment with BALSS, the porcine liver cells' survival rate in the cell suspension was examined by trypan blue stain and AO/PI fluorescent stain once an hour and the patient's heart rate, blood pressure and respiration condition were measured with multi-functional monitor and the blood biochemical indexes for liver function, kidney function and blood coagulation function were analyzed.

Clinical data

The general condition and the therapeutio methods for the six patients with live r failure are shown in Table 1. Among these patients, cases 1, 3 and 5 were chronic viral hepatitis, their liver function decompensated and developed liver failure; cases 2, 4 and 6 were ALF caused by partialliver excision after surgery, viral hepatitis or drug toxication, respectively. Before the treatment of TECA-HALSS, all the patients suffered from various degree of hepatic coma. They were treated by TECA-HALSS for 6-7 h, and with conventional medicines as well.

Table 1 Clinical data of six patients with liver failure

No	M/F	Age	Diagnosis	General condition	Program of treatment	*t* (treatment)/h
1	M	50	Liver cirrhosis (decomp ensation) HCC, ALF	Hepatic encephalopathy lethargy	Whole blood CA & TECA-BALSS	2.5
2	F	50	Post operation of cancerof biliary duct, ALF, ARF	Hepatic encephalopathy lethargy	Plasma CA & TECA-BALSS	2+4
3	M	32	Hepatitis B Liver failure	Hepatic encephalopathy TECA-BALSS	Plasma CA &	2+4
4	F	43	Acute viral hepatiti sfulminant hepatic failure	Hepatic encephalopathy (stage IV)	PE and TECA-BALSS	2+4
5	M	32	Hepatitis B (decompens ation) Liver failure	Hepatic encephalopathy (stage IV)	PE and TECA-BALSS	2+5
6	F	34	Drug induced hepatic injury, liver failure	Hepatic encephalopathy lethargy	PE and TECA-BALSS	2+5

RESULTS

The swine liver cells obtained and cultured

The obtained average of porcine liver cells was (1.0-3.0)×10^{10} from each swine liver by our modified enzymatic separation method. The survival rate of the cells was 85%-93% by trypan blue stain and AO/PI fluorescent stain. After cultured in TECA-BALSS bioreactor for 6 h, the survival rate of cells still remained 70%-85%.

Changes in basic physiological indexes

During the TECA-HALSS treatment, heart rates, blood pressure and respiration condition in all the six patients remained stable without thrombosis and bleeding. Those who were in the state of drowsiness or coma before the treatment improved their appetite significantly and regained consciousness, some patients resumed light physical work in a short period after the treatment.

Changes in biochemical indexes of blood

At the end of the treatment with HALSS, the patients' liver function related biochemical indexes, such as the levels of NH 3, ALT, TB and DB were significantly decreased. Blood coagulation was improved, the PT was shortened and PTA was raised. There were no significant changes in the levels of the patients' main serum electrolytes (K^+, Na^+ and Cl^-) during the treatment.

Typical cases

Case 2 was a patient with ALF complicated with acute kidney failure after left half liver excision. After twice blood dialysis, the patient's renal function was improved temporarily, but she was in the state of hepatic coma with drowsiness. At the 7th day after operation, she received the treatment of TECA-HALSS with plasma-carbon absorption for 2h and plasma-BALSS treatment for 4h. The patient's blood ammonia level was returned to normal and she regained consciousness (Table 2). Two days after the treatment of HALSS, she had normal liver function and receive d blood dialysis for the renal disfunction. Because of economic reasons, she was discharged from the hospital voluntarily.

Table 2 Changes of pre- and post-treatment by TECA-HALSS in case 2

Parameters	Pre-HALSS	Post CA	4 h post-BALSS	2 d post-HALSS
NH_3(μg/L)	134	93	30	53
ALT (IU/L)	64	27	29	53
AST (IU/L)	69	47	269	97
TB (μmol/L)	495	423	400	405
DB (μmol/L)	240	204	198	350
UN (mmol/L)	41	35.7	36.6	37
Cr (μmol/L)	651	121	407	
K^+(mmol/L)	4.99	4.66	4.47	4.9
Na^+(mmol/L)	132	131	133	131
Cl^-(mmol/L)	99.6	104	104	96
Mentality	Lethargy	Lethargy	Consciousness	Consciousness

Case 4 was a patient with acute severe viral hepatitis complicated with fulminant liver failure and stage IV hepatic coma and PTA 13%. The liver was found shrink and diffused liver damage by ultrasound B examination. After coma for three days, she received T ECA-HALSS with 2.5 L plasma exchanged and 4 h of BALSS treatment. After the treatment, the levels of ALT, TB, DB and ALP were significantly decreased and PTA value increased rapidly (Table 3). The patient experienced superficial coma one day and regained consciousness and could eat food two days after treatment. Five days later, her abilities of calculation and orientation became normal and eight days later, she was discharged from the hospital. Two months' follow up showed that her general condition was good and she could do some light physical work, his liver function parameters were within normal range.

Table 3 Changes pre- and post-treatment by TECA-HALSS in case 4

Pre-HALSS		HALSS			Post-HALSS			
		Post-PE	BALSS 2 h	BALSS 4 h	d 1	d 2	d 4	d 7
NH3 (μg/L)	78	114	101	108				
ALT (IU/L)	1352	408	390	336			225	146
AST (IU/L)	142	45	629	751			45	63
TB (μmol/L)	17.11	7.23	9.99	9.22			16.95	29.18
DB (μmol/L)	12.03	5.08	6.25	5.72			12.74	21.26
TP (g/L)	69.8	54.5	48.1	43.5			48	56.2
ALB (g/L)	34.29	31.8	28.5	25.6			23.3	24.6
ALP (IU/L)	297	144	140	115			176	213
PTA (%)	13.15				21.6	29.6		48.8
Mentality	Deep coma	Deep coma	Deep coma	Deep coma	Superficial coma	Consciousness		

DISCUSSION

It is well known that ALF has a very high morbidity and mortality rate. The conventional medical treatment was hard to achieve satisfied outcomes since liver cells possess the strong ability of regeneration. Therefore, if a full liver support therapy can be provided to keep the patients alive and avoid severe complications to occur, the patients' liver function can recover spontaneously or win the time for liver transplantation. The research about using artificial means to temporarily support the liver function has attracted worldwide attention. Many years of research has been carried out on non-bioartificial liver support systems, which detoxicate nonspecifically or specifically by using absorption, plasma dialysis, blood or plasma exchange and so on. In this way, it can eliminate the possible toxic substances in the blood so as to provide a chance for liver cells to regenerate and repair. But some reports indicated that these methods did not work well in treating liver failure. For example, carbon absorption can only nonspecifically detoxicate part of the toxic substances in the blood and can not greatly increase the survival rate of patients with liver failure. Although replacing a large quantity of patients' plasma (3-4L) within a short time can correct one third of the biochemical indexes related to liver function, this effect can only last 1-3 days and the patients' mental malfunction can not be improved significantly[35-37]. Case 3, received 8 times of plasma exchange. Each time after plasma exchange, the patient was still listless and drowsy, his biochemical indexes of liver function were corrected by only one third to one fourth, and deteriorated again within 1-3 days. At the end of TECA-HALSS treatment, the patient turned from drowsy to conscious, he also asked for food and walked out of the treatment room without help. The patient's blood parameters of liver function remained normal for almost 20 days. Therefore, it is believed that non-bioartificial liver support system could not be enough for substituting the complicated function of liver. In recent years, newly developed bioartificial liver support systems use exnogenous liver cells to provide the functions of biosynthesis, detoxication and biotransformation. Our previously developed TECA-BALSS has been proved to be safe and effective as a temporary replacement of liver function in the treatment of ALF in dogs caused by acetaminophen[26]. The porcine liver cells cultured in TECA-BALSS possess liver cell functions, such as biosynthesis, detoxication and biotransformation. The ALF patient's blood circulated through BALSS and reacted with the porcine liver cells through the semipermeable membrane of the hollow fiber tubes in BALSS[31,38-39]. Our and other studies showed that porcine liver cells in BALSS, functioning as a temporary replacement of liver, could win a period of time for the patients or animals with liver failure to regenerate and repair their liver[29,40]. Our research found that t he toxic substances of the ALF patients' blood can damage the porcine liver cells[41]. In this experiment, we used non-bioartificial liver methods (carbon absorption and plasma exchange) for reducing the toxic substances first and later used BALSS to exert biological function of liver cells, i.e., TECA-HALSS. The results from 6 cases of acute and chronic liver failure showed that TECA-HALSS could significantly improve the liver function by lowering the levels of blood NH 3, ALT, TB and DB and increasing PTA. Our preliminary result indicated that BALSS could significantly improve the patient's consciousness and the effect persisted longer than by plasma exchange.

According to the reports both domestic and overseas, the major use of HALSS is for the patients with ALF caused by various reasons, such as viruses, drugs and ischemia[42-45]. Through temporary liver function substitution, HALSS treatment wins the time for liver cells to regenerate and repair and compensatie liver function. However, for the patients with chronic liver failure, the main propose of HALSS treatment is to provide the bridge to liver transplantation, especially for the patients with hepatic coma staged III-IV[30,46-47]. BALSS treatment can be carried out in two ways: blood perfusion and plasma perfusion. Our results suggested that it preventing thrombosis by the way of plasma infusion is favored in HALSS. This can also reduce the dosage of heparin, which is very important to the patients with liver failure complicated with coagulation malfunction. The times and duration of HALSS treatment depend on the patients' biochemical indexes of liver function, mental consciousness and so on. It was reported that some patients received HALSS treatment as many as over 10 times[48-50]. The results from our experiment and others indicated that HALSS treatment is safe and practical. During the treatment, to monitor the basic physiological indexes of the patients and supplement blood instantly are suggested. Other authors found that after the treatment with HALSS, there were no significant immune reactions and no negative effect on the following liver transplantation. No immune factors directly influence the patients' prognoses. The results suggested that TECA-HALSS could be a rapid, safe and efficacious method to provide temporary liver support for the patients with ALF.

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