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Preliminary Research of Off-Line Bioartificial Liver on Patients with Hbv Related Acute-On-Chronic Liver Failure

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Abstract

Objective: The study aims to construct an off-line bioartificial liver support system (off-line BAL) with human liver cell line, and explore it's safety and effect in patients suffering with HBV-related acute on chronic liver failure (ACLF).

Methods: The off-line BAL was constructed with cultured HepG2 cell. Twenty patients with HBV-related ACLF were randomly separated into the two groups. Patients in the treatment group were dealt with plasma exchange (PE) first and then BAL treatment. The control group received a therapy of PE only . The clinical parameters were assessed at different times and survival rate was evaluated at 3 months.

Results: In the treatment group, 9 patients' general conditions and clinical symptoms were improved, total bilirubin decreased about 44.27%, MELD scores decreased to 21.71 from 24.26, prothrombin activity (PTA) increased to 48.97%, and there was a significant difference between pretreatment and post-treatment.

Compared to the control group, PTA increased dramatically (51.02% *vs.* 37.24%; P=0.0477) at 4 weeks and MELD score decreasedsignificantly (21.71 *vs.* 24.47; P=0.0409) at post-treatment in BAL groups. During the 12 weeks, the survival rates were 70% and 50% (P=0.3613) in the treatment and control groups. No severe adverse events occurred and no liver tumor was found following three years of observation.

Conclusions: The off-line BAL may be safe for patients with liver failure. It can improve the patients' clinical conditions and laboratory parameters, but it has no obvious benefit compared to PE treatment. The routine clinical application still needs further evidence.

Keywords: Liver failure; Bioartifcial liver; HepG2; Treatment

Introduction

Liver failure is a severe clinical syndrome characterized by hepatic encephalopathy, ascites, icterus, coagulation disorder due to a variety of acute or chronic injuries induced by various causes, such as hepatotoxic drugs, alcohol consumption, and hepatitis virus infection [1-3]. In China, Hepatitis B virus (HBV) infection accounts for the highest proportion of hepatitis cases. Some chronic hepatitis B patients may rapidly progress toward acute-on-chronic liver failure (ACLF), and liver transplantation is considered the standard treatment for these patients. However, several limitations, such as lack of donor organs, operative damage, risks of rejection and high costs have restricted the use of liver transplantation in many ACLF patients.

Terefore, new alternative therapy to delay or improve disease progression of ACLF is urgently required. Cell therapies have been suggested and extensively studied in the world [4]. Among them, hepatocytes based therapy for liver failure has been attracting great attention [4,5]. Several types of extracorporeal artifcial livers have been used to treat liver failure patients including physical and bioartifcial liver (BAL) support systems [6].

The physical artifcial liver system can improve hyper-bilirubinemia and hepatic encephalopathy. However, these roles are temporary, and clinic trials have shown a benefit to the short-term survival rate of liver failure patients [7]. To acquire replacement of hepatic function, researchers have tried to develop BAL devices [2,3,8].

BAL is equipment through which blood plasma is circulated over living liver cells or liver cell line cultured in a bioreactor. The use of BAL with living cells can provide patients with functions of metabolism, detoxication and synthesis [2]. At present, on-line BAL is common in clinical trials in which the blood plasma separation devices and cell based bioreactor are linked; however, anticoagulant therapy may have impacts on patients' coagulant system in the course of therapy. Up to now, no bioartifcial liver has been applied for treating patients in clinics due to its unsatisfactory efect in improving the liver function [8,9].

In the present study, we successively established the cell line expressing human augmenter of liver regeneration (hALR). A total of 800 million HepG2 hALR cells were cultured in bioreactors for 96 hours, and found it can keep hepatocyte - specifc synthesis and metabolism functions [5,10].

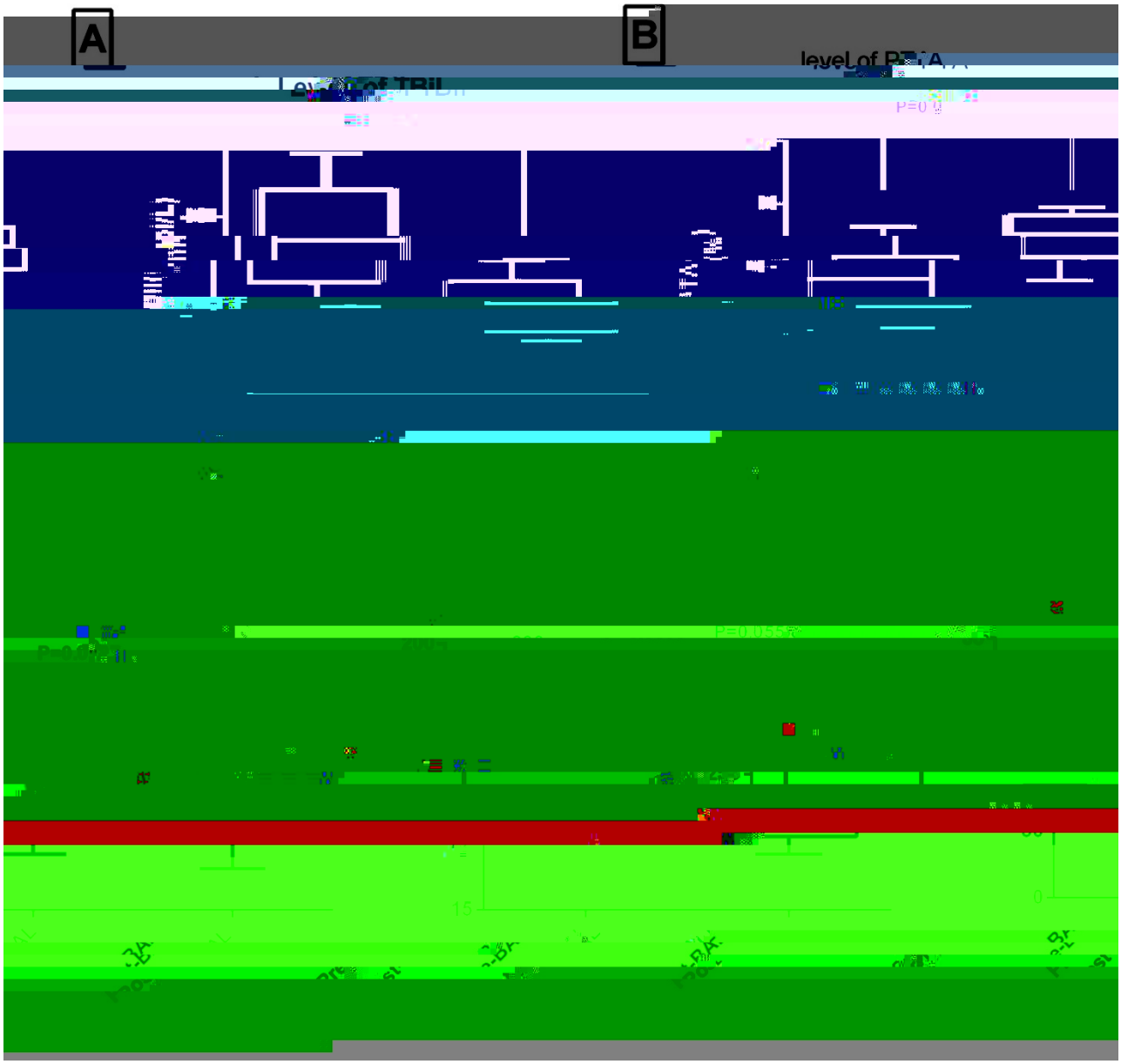
established previously in our lab [10]. Prior to use, bioreactors were rinsed with 500 mL 0.9% sodium chloride for three times (Figure 2).

2. Plasma exchange for the frst time: Blood access was set up through a double-lumen catheter (Arrow International, Inc. PA, US) via the jugular vein of the patient with liver failure. PE was manipulated with EC-40W plasma separator (Asahi Kasei Co., Japan) in artifcial machine (EQUA-SMART, Italy) with blood fow velocity 100 mL/min and exchange rate 10~15 mL/min. Te total volume of discarded blood plasma was about 2800 mL.

3. Extracorporeal bioartifcial liver treatment: Extracorporeal bioartifcial liver supporting system was constructed as shown in

Figure 2. Afer

Prognostic evaluation: Improved- patients who were discharged from our hospital because clinical symptoms improved and hepatic


A
B

8	T	Male	54	ACLF	24.61

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