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The Concept of Artificial Liver Support by Using the Extracorporeal Circulation System

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In this study, a basic research on artificial liver was performed for its application to people on the waiting list of liver transplant or patients with hepatic insufficiency. Artificial livers are generally classified into mechanic type, bioartificial type, and hybrid type. An extracorporeal circulation device was examined herein, which is indispensable in the application of an artificial liver, for its effectiveness in supporting the recovery of liver functions. Extracorporeal circulation system is a treatment and life-support system which sends out the patient's blood, removes toxicity by various methods, and then sends the blood back to the interior of the body. This study used an extracorporeal circulation system which enables the Plasma Perfusion by CVVH method, and applied the program of Bioateco corp. Animals with acute hepatic insufficiency were produced to apply the extracorporeal circulation device. As a result, their ammonia, bilirubin, SGOT, SGPT, and bile acid levels rose, confirming the liver function restoration in the experimental animals.

Keywords: Extracorporeal circulation system, Plasma perfusion, Artificial organ

1. INTRODUCTION

Artificial organs refer to a device or organ made based on bionic technologies to substitute for human body organs. Artificial organs are largely divided into engineering technology-based mechanical artificial organs, tissue engineering-based regenerated organs, and cell-using artificial organs.

Presently, artificial organs are most actively developed and applied to human body via transplant. They are not to replace organs but to temporarily improve the status. Still, they are very important for the maintenance of life. Post-operational cardiogenic shock in patients with cardiovascular disease require the use of an extracorporeal life support system in many cases [1]. Also, the development of continuous ambulatory peritoneal dialysis may change the direction of an artificial kidney. However, unlike heart that simply functions as a blood-circulating pump or kidney that filters out waste, liver performs more complicated functions such as protein synthesis, metabolism, and detoxification, which are hardly substituted by a pump or dialysis filter [2]. In the US, the number of patients with liver-related disease was in several hundreds of thousands [3]. However, in South Korea, the number of liver transplantation receivers is extremely few. As for fulminant hepatic failure with the fatality rate of 80%, liver transplant is the only recognized effective measure; but, only too few livers are donated to be given to more [4]. For this situation, artificial livers are developed, which can function as liver until the liver transplant or regeneration [5,6].

The artificial liver system is structured to run the patients' blood through by cultivating human liver cells or charging animal liver cells into bioreactor [7,8].

This research examined the effects of an auxiliary artificial liver device utilizing an extracorporeal circulator that removes

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blood toxins while circulating blood along the artificially built circuit outside of the body.

2. EXPERIMENTS

2.1 Extracorporeal circulation

The extracorporeal circulator sends blood outside of the body through a tube inserted in blood vessels, circulates blood along the artificially-built extracorporeal circuit to detox or supply oxygen, and injects the blood back into the body. One of the most widely utilized extracorporeal circulators is in-operation artificial heart-lung machine. Currently, other techniques of cardiopulmonary bypass utilizing blood vessels outside of the thoracic cage is also being researched.

The idea of extracorporeal circulation in artificial livers is partly from the principle of hemodialyzer used as artificial kidneys. Hemodialyzer is a device that removes blood waste if a person is exposed to diverse diseases due to kidney malfunction or is unable to live a normal life.

It removes waste by sending the patient's blood outside of the body, through a controlled volume pump to filter out water and waste, and then injecting the blood back into the patient's body. In this process, the hollow-fiber filter consisting of semi-transmitting films is used, which have numerous fine holes to filter out the waste.

In this research, the extracorporeal circulator (HF440, Infomed corp., Switzerland) employed the plasma perfusion method after modifying the CVVH (continuous venovenous hemofiltration). In the plasma perfusion circuit that absorbs plasma toxin materials, blood passes through the hollow-fiber form of plasma filter and separates the plasma.

The separated plasma passes through the absorption filter for detoxification and then meets the patient's blood again to return. In this manner, clotting which takes place when blood meets oxygen can be prevented. Figure 1 shows the diagram of using the plasma perfusion circuit in HF440 as an extracorporeal circulator.

2.2 Experimental model

This research used 12-week-old hogs with 30 kg of weight. Hogs without a visible wound were selected and blood tested to check for the normal health status. For their stabilization, hogs were kept in a breeding room maintaining 21~23℃ temperature until fully rested. During this stabilization period, the experimental animals were allowed to take feed and water freely but these were limited 24 hours prior to the experiment.

Carbon tetrachloride was injected into the hogs to produce experimental animals with impaired liver function. For liver function impairment, carbon tetrachloride was adjusted within 50~100 mg/kg in its volume according to the sizes and characteristics of hogs and was mixed with corn oil to be injected for 3 rounds in the abdominal cavity.

The carbon tetrachloride-injected experiment specimens with impaired liver functions were then anesthetized by the intramuscular injection of 1:1 mixture of zolitil and rompun. During the experiment, anesthesia status was maintained based on the gas mixture of sevoflurance, nitrogen, and oxygen via an anesthetizing instrument (Fabius, Drager Corp., USA).

Their breathing was maintained at constant, and the patient monitors (InteliVue MP20, Philips Corp. Germany) were connected to the experimental animals to monitor their status in real time. Medicine was injected when their blood pressure dropped,

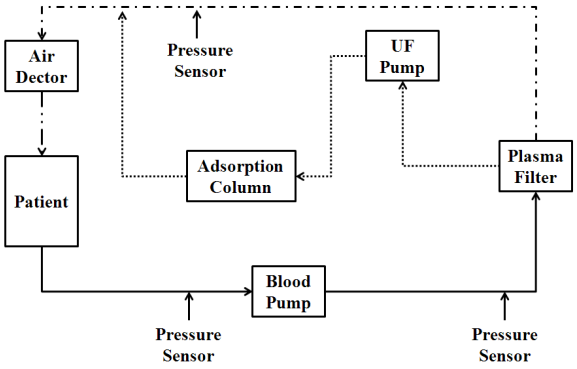

Fig. 1. The plasma perfusion of extracorporeal circulation.

to maintain their stability until the end of the experiment.

The experimental animal's blood and serum tests in stable conditions showed ammonia 345 μg/dL, bilirubin 0.1 mg/dL, SGOT (Serum Glutamic Oxaloacetic Transaminase) 2,343 U/L, SGPT (Serum Glutamic Pyruvate Transaminase) 112 U/L, and bile acid 27.9 μmol/L.

3. RESULTS AND DISCUSSION

The first filter used in the extracorporeal circulator was a hollow fiber-type plasma separation filter (LF030, Infomed Corp., Switzerland). The second filter was absorption filter (BR-350, Asahikasei Kuraray Medical Corp., Japan). The double filtration tubing set (Two-Lumen Central Venous Catheterization Set, ARROW Corp., Canada) was used to connect the experimental animals with extracorporeal circulator for plasma perfusion. Then, the bioateco set program was operated. To minimize the contact between blood and air before the experiment, a controlled volume pump was used to remove intra-tube air with normal saline. To prevent blood clotting, the tubing was coated with heparin. Heparin 1.25 m./min was injected into the tubing to prevent clotting of its blood or blood returning to it. The in-blood plasma amount is approximately 60%. But in consideration of plasma amount remaining in the blood returning into the body after detoxification, the amount of plasma separated by the plasma filter was controlled not to exceed 30%. The blood pump rate was initially set at 30ml/min, and once stabilized, it was raised to 80 ml/min. Plasma/blood rate also started from 10% and then was increased up to 30%. The experiment was conducted for 4 hours. The experimental animals were maintained stabilized until the termination of experiment. To prevent increase in vein pressure, heparin was partially injected. No blood hematolysis or clotting was witnessed. After termination of the experiment, blood inside of the experimental specimens was sampled along with the blood returning vial HF440 to inspect ammonia, bilirubin, SGOT, SGPT, and Bile acid.

The results are shown in Figs. 2, 3, 4, and 5. The experimental specimens in this research were injected with carbon tetrachloride in the abdominal cavity to impair the liver functions, and their liver dysfunction was confirmed by the blood test.

Bilirubin generated in spleen by heme metabolism was sent to the liver. Liver cells changed it in the form of bile to be stored in gall bladder, and then it was released to duodenum. Acute and chronic hepatitis, viral hepatitis, alcoholic liver disorder, liver cell metabolism disorder, etc. could increase in-blood bilirubin levels. In this research, small amount of bilirubin was found; but after using the extracorporeal circulation system, it was not found any more.

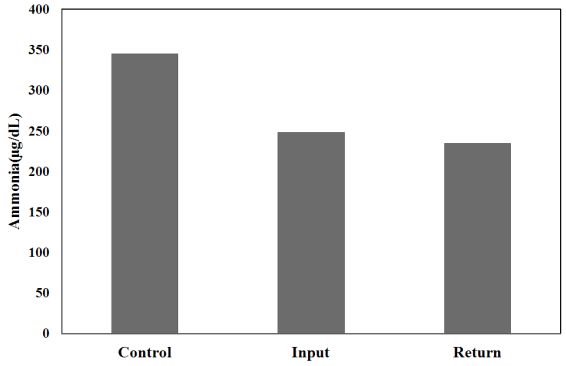

Fig. 2. The changes in ammonia levels.

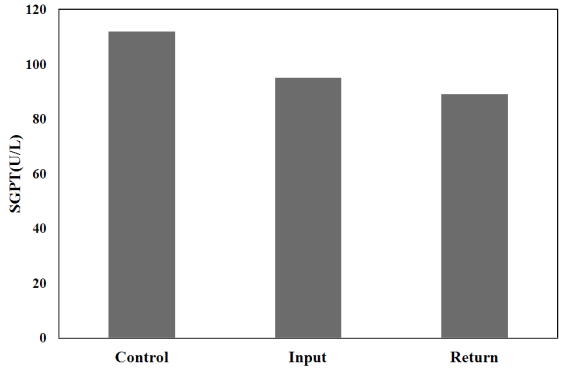

Fig. 4. The changes in SGPT levels.

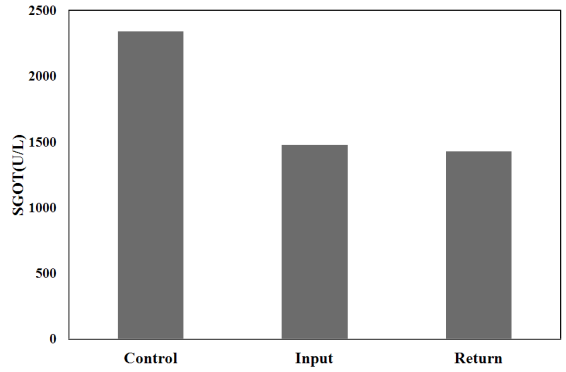

Fig. 3. The changes in SGOT levels.

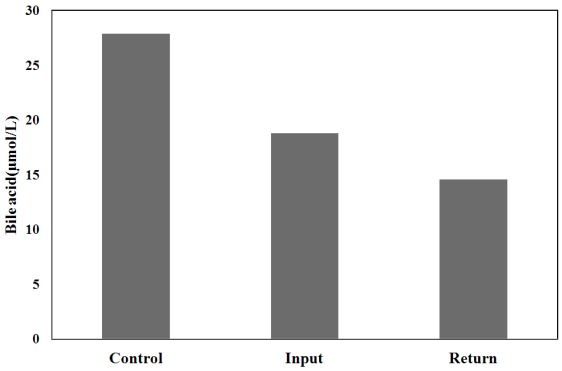

Fig. 5. The changes in bile acid levels.

Ammonia is a compound of nitrogen and hydrogen. If accumulated inside the body, it could cause a hepatic encephalopathy. Ammonia is one of the wastes generated in the process of turning protein into energy. It is an alkaline toxin that must be excreted from the body. If a human body is exposed to ammonia for a longer period, it could harm the eyes, liver, kidney, etc. In addition, ammonia could bring hepatic encephalopathy possibly leading to death [9]. Figure 2 shows changes in ammonia before and after the use of extracorporeal circulation system.

Normal ammonia level is within 19~87 μg/dL. The in-blood ammonia level in the carbon tetrachloride injected experimental animals was found to be 345 μg/dL. After the extracorporeal circulation system, the ammonia level in blood returning to the body was 235 μg/dL, indicating improvement.

SGOT is one of the hepatic cell enzymes which increases in acute liver impairment, and its normal range is 0~35 U/L. Figure 3 shows SGOT changes. The control was measured higher at 2,343 U/L, but after the extracorporeal circulation system, it was found to be 1,431 U/L, indicating a strong effect.

SGPT is an enzyme inside of the liver cells, and its normal range is 0~35 U/L. When it enters into the blood while liver cells are damaged, SGOT surges in acute liver impairment just as viral hepatitis. Figure 4 shows changes in SGPT. The SGOT/SGPT ratio is sometimes used to identify the cases of liver damage [10,11].

Bile acid is produced from liver cholesterol and involves in intra-body cholesterol metabolism, sugar metabolism, and nucleic acid metabolism. Bile acid is circulated into the liver through reabsorption in the intestine. The circulated bile acid facilitates bile secretion in the liver, cholesterol synthesis, etc. Thus, bile acid is one of the significant tests use as an inference for recovery from liver disease. The normal range of bile acid is below 6 μmol/L, but as for the experimental animals with liver malfunction, it was measured at about 30 μmol/L. After applying the extracorporeal circulation system, the level was 14.6 μmol/L which shows considerable improvement.

4. CONCLUSIONS

This research investigated the effects of extracorporeal circulation system used for artificial livers. Carbon tetrachloride was injected into the experimental animals to produce a hepatic encephalopathy status, and the effects on the recovery of liver function was experimented. Pre/post-extracorporeal circulator levels of ammonia, bilirubin, SGOT, SGPT, and bile acid were compared herein. The post-circulator levels were remarkably lower, which indicates that the experimental animal's blood was removed as it passes through the extracorporeal circulator. Based on the research findings, the extracorporeal circulator could be an alternative life support for patients waiting for a liver transplant, the patients with acute or chronic hepatic insufficiency waiting for a liver donor, or people in the process of liver function recovery.

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