Study Protocol Open Access

Comparison between the internal and external pressure filtration methods of cell-free and concentrated ascites reinfusion therapy to treat refractory cancerous ascites

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Abstract

Background: Cell-free and concentrated ascites reinfusion therapy (CART) was approved by the National Insurance Scheme in 1981 in Japan and has since been used as a treatment modality for refractory ascites. Two filtration methods may be used for CART: the internal and external pressure filtration methods. However, the precise characteristics of each method are unknown.

Methods: Ascitic fluid will be obtained by puncture from patients with refractory cancerous ascites. The quantity of fluid obtained from each patient will be divided in half, and each half will be processed using either the internal or external pressure filtration method. The primary endpoint will be the time required for the transmembrane pressure to reach 500 mmHg. The secondary endpoints will be serial changes in the weight of the ascitic and filtered fluid, serial changes in the pressure at the inlet and outlet of the filter, measurement of the components of the ascitic and filtered fluid, and observation of the filter by visual inspection and light and electron microscopy.

Conclusion: This trial may clarify the characteristics of the two filtration methods.

Trial registration: UMIN000025382.

Keywords: Cell-free and concentrated ascites reinfusion therapy, Internal pressure filtration method, External pressure filtration method

Introduction

The management of symptomatic malignant ascites involves abdominal paracentesis, diuresis, peritoneovenous shunt placement, transjugular intrahepatic portosystemic shunt placement, and cell-free and concentrated ascites reinfusion therapy (CART). CART is a treatment modality whereby unwanted components such as cancer cells and bacteria are removed from ascitic fluid using a filtration membrane, and essential proteins are allowed to remain and become concentrated. The representative article describing CART procedures was published in 1977.[1] CART was approved by the National Insurance Scheme in 1981 in Japan and has since been used as a treatment modality for refractory ascites. CART comprises three steps: paracentesis, removal of cell components from ascitic fluid, and reinfusion of the fluid obtained through this process. Increased circuit pressure and clogging are the main technical problems associated with CART and may cause premature termination of the therapy. The most common adverse events during reinfusion are fever and chills. Filtration may occur in two directions: inside-out and outside-in. Post-treatment surveillance in Japan revealed that the inside-out filtration method was performed in 89.3% of facilities and that the outside-in method was performed in 10.7% of facilities.[2] The inside-out filtration method is performed in our facility. Whether the frequency of technical problems or adverse events differs between the two filtration methods is unknown. In this study, we plan to evaluate the efficacy of both filtration methods using the same cancerous ascitic fluid and compared the characteristics of each method.

Method

This will be a single-center, non-blinded study. The quantity of ascitic fluid obtained from each patient will be divided in half, and each half will be processed using either the external (Figure 1) or internal (Figure 2) pressure filtration method. We will use a polyethylene AHF-MOW filter (Asahi Kasei, Tokyo, Japan). The inner diameter of the hollow fiber measures 280 μm, the membrane thickness is 50 μm, and the effective membrane surface area is 1.5 m^2. The fluid will be filtered with a flow rate of 50 mL/min set by the pump. Filtration will be stopped when the transmembrane pressure (TMP) reaches 500 mmHg, which is the maximum endurable pressure noted in the document provided by the manufacturer. The time required to reach the maximum TMP will be recorded. Next, the filtered ascitic fluid will be concentrated using the AHF-UP model (Asahi Kasei). We will use the Plasauto-LC blood purification apparatus (Asahi Kasei). A new filter will be used when untreated ascites remains. Our study has been approved by the ethics committee of Fujita Health University School of Medicine (UMIN registration number UMIN000025382).

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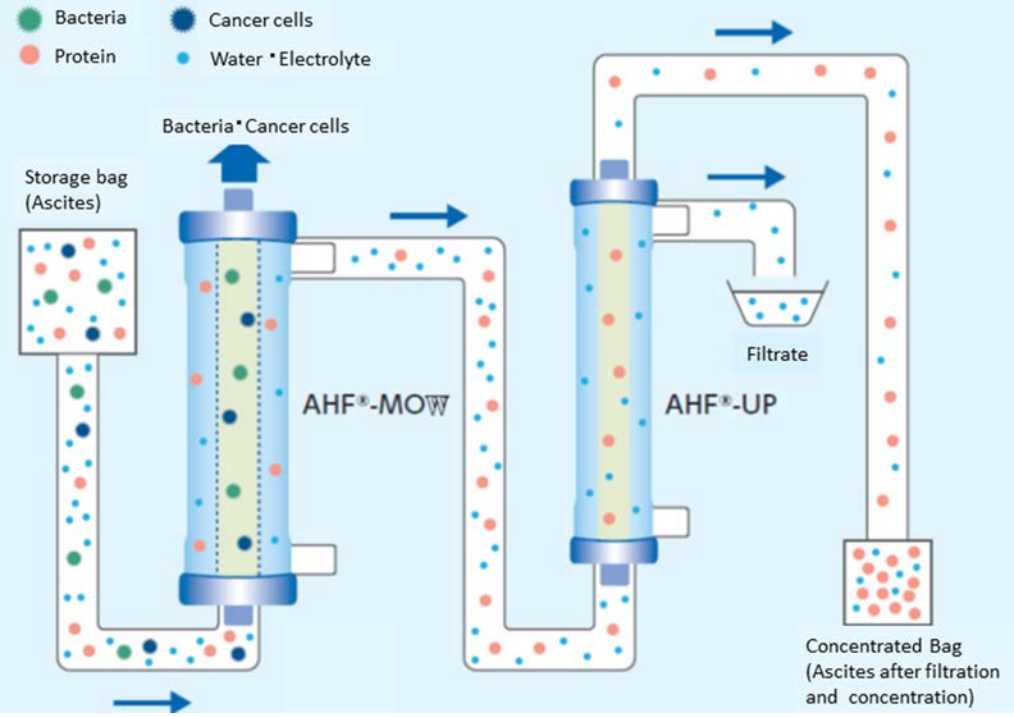

Figure 1 Ascites is filtered from the outside to inside in the external pressure filtration method[3]

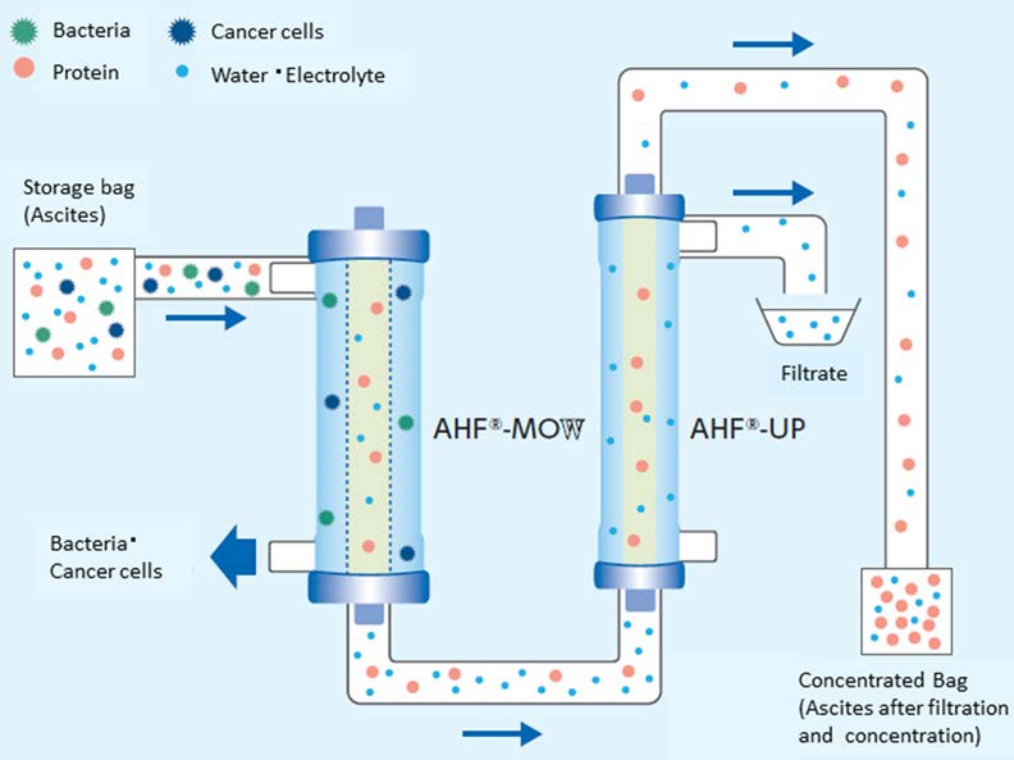

Figure 2 Ascites is filtered from the inside to outside in the internal pressure filtration method[3]

Inclusion criteria

Patients with intractable ascites who meet the following criteria will be included:

1) Intractable cancerous ascites with indications for CART is present
2) Informed consent is obtained from the patient after he or she has received a detailed explanation about the study.

Exclusion criteria

Patients who meet the following criteria will be excluded:

1) Endotoxin detected in the patient's ascitic fluid using a test puncture.
2) Severely immunocompromised patients such as those who have undergone bone marrow transplantation.
3) Patients with a peritoneovenous shunt (peritoneal–subclavian vein bypass).
4) Patients with a transjugular intrahepatic portosystemic shunt.
5) Infection: syphilis, presence of hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus, human immunodeficiency virus 1 or 2, human T-lymphotropic virus type 1.
6) Patients considered to be inappropriate for the study as determined by a doctor.

Discontinuation criteria

The trial will be discontinued for patients who meet the following criteria:

1) When participants offer to withdraw from the study or do not provide consent.
2) When the clinical study cannot be continued because of adverse events, including the following, as determined by a doctor in charge:
   - Ascitic fluid cannot be collected because of adverse events such as hypotension.
   - A doctor in charge determines that unpredicted and sudden adverse events could occur.
3) When the clinical study needs to be stopped.
4) When a doctor in charge determines that discontinuation of the study is appropriate.

Sample size

The planned sample size has been set at 21 patients. If fewer than 3 of the 21 patients develop a significant increase in the TMP, the study will be continued until the number of such patients reaches 3. Because the potential statistical variations are presently unknown, the planned number of patients has been set according to the number that could be theoretically treated at our hospital. A minimum of three patients in whom the TMP reaches 500 mmHg is needed to evaluate the primary endpoint. Thus far, a significantly increased TMP has occurred in 16% of patients treated at our hospital. CART for cancerous ascites was performed in 23 patients last year. From these data, we have set the number of included patients at 21.

Primary endpoint

The primary endpoint of the study is the time required for the TMP to reach 500 mmHg.

Secondary endpoints

The study has several secondary endpoints:

- Serial changes in the weight of the ascitic and filtered fluid (Schedule c). The weight of the ascitic fluid before and after filtration will be serially measured using a gravimeter.
- Serial changes in pressure at the inlet and outlet of the filter (Schedule d).
  The pressure at the inlet and outlet of the filter will be measured.
- Components of the ascitic and filtered fluid (Schedule e). Total protein, albumin, blood cells, other cell types, fibrinogen, bilirubin, haptoglobin (free hemoglobin), Na^+, K^+, and Cl^- will be measured.
- Observation of the filter (Schedule f). Following filtration, the filter will be observed by visual inspection and light and electron microscopy.
- Schedule

	Before drawing ascitic fluid	After drawing ascitic fluid	After division of ascitic fluid	During filtration of ascitic fluid	After filtration of ascitic fluid	After concentration of ascitic fluid
a.	○					
b.	○					
c.		○	○	○	○	
d.				○		
e		○			○	
f.						○

a. Obtain informed consent.
b. Evaluate indications for treatment.
c. Measure serial weight of ascitic and filtered fluid.
d. Measure filtration pressure of ascitic fluid.
e. Measure components of filtered ascitic fluid.
f. Observe the filter after completion of filtration.

Statistical analysis

Differences between the two groups will be evaluated by the Mann–Whitney U test. Statistical significance will be set at $P<0.05$.

Discussion

In the internal pressure method, filtration is performed from the inside to outside. When using this method, the flow velocity on the membrane surface is speculated to be higher than that in the external pressure method. However, the membrane surface area is greater in the external than internal pressure method. Whether each characteristic contributes to the elevated pressure or to the production of cytokines by cells remains unknown. Only one published report has compared the internal and external pressure filtration methods of CART.[4] In that study, the vertical fluid pressure was utilized to filter ascitic fluid in patients with liver cirrhosis. The authors compared the amount of ascitic fluid recovery and total protein recovery. Their results demonstrated no significant differences in the amount of ascitic fluid recovery and total protein recovery between the two methods. Ascitic fluid from patients with liver cirrhosis has fewer cells and mucous components than that obtained from patients with cancer. CART is now widely used for patients with malignant ascites. Various symptoms related to malignant ascites improve following CART.[2] The participants in our study are patients with cancer. Clogging of the membrane or elevated pressure during the procedure could become problematic. Therefore, our primary endpoint is the time required for the TMP to reach 500 mmHg. One of the secondary endpoints is measurement of the components of the ascitic and filtered fluid. A higher recovery of albumin is essential for CART. Blood cells are associated with the release of proinflammatory cytokines during filtration. Fever is a major adverse event associated with CART. Borzio et al.[5] reported that 12% of their patients who received concentrated ascites developed fever and chills. It is speculated that polymorphonuclear leukocytes or lymphocytes attach to the filter, and the shear stress caused by filtration activates blood cells. These activated blood cells release proinflammatory cytokines such as interleukin-6, which is associated with the development of

fever.[6,7] Fibrinogen is associated with clogging of the filter. Bilirubin and haptoglobin are measured as markers of hemolysis. The weight and pressure as other secondary endpoints are measured to evaluate the efficiency of filtration. The clogging state and adhesion of cells are revealed by observation of the filter.

This trial may clarify the characteristics of the two filtration methods.

Conflict of interest

No conflict of interest is declared.

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