Outcomes of Intermittent Infusion Hemodiafiltration in Patients with Cardiac Hypofunction on Maintenance Hemodialysis

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Keywords

Cardiac hypofunction · De Jager-Krogh phenomenon · Plasma refilling

Abstract

Background: Following the onset of heart failure symptoms, fluid removal is usually intensified, but patients with decreased cardiac function may develop sudden hypotension due to poor plasma refilling and functional impairment of the mechanisms that maintain blood pressure. In these patients, removal of fluids then becomes difficult. Impairment of the mechanisms that maintain blood pressure can be treated with vasopressors, but intermittent infusion hemodiafiltration (I-HDF) may be effective for managing poor plasma refilling. Thus, here I-HDF was performed in patients with cardiac hypofunction who were undergoing maintenance hemodialysis (HD) in order to assess the clinical effects. **Summary:** Participants were 5 patients with cardiac hypofunction on maintenance HD. HD and I-HDF were performed for a total of 6 months each. A comparison was made of changes in dry weight (DW) and cardiothoracic ratio (CTR), blood test results, echocardiography findings, plasma refilling rate (PRR), and tissue blood flow. During I-HDF, a decrease in DW was achieved and CTR was significantly improved. Echocardiographic findings showed that left ventricular diameter im-

proved significantly during I-HDF. Higher PRR values and increased tissue blood flow were observed during I-HDF compared with HD. Intermittent infusions during I-HDF prevented organ ischemia and suppressed the De Jager-Krogh phenomenon. This may be associated with the promotion of stable plasma refilling. **Key Messages:** Excessive fluid retention is a cause of heart failure symptoms. I-HDF facilitates removal of excessive fluid and thereby possibly contributes to the improvement of cardiac function.

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Introduction

When the cardiac shadow is enlarged and symptoms of heart failure such as orthopnea appear, the dry weight (DW) setting is lowered and fluid removal is intensified. However, if patients have impaired cardiac function, intradialytic hypotension (IDH) frequently occurs due to poor plasma refilling and functional impairment of the mechanisms that maintain blood pressure. Thus, removal of fluids becomes difficult in these patients. Function impairment of the mechanisms that maintain blood pressure can be treated with vasopressors, but intermittent infusion hemodiafiltration (I-HDF) may be effective for managing poor plasma refilling. To examine this

hypothesis, I-HDF was performed in patients with cardiac hypofunction who were on maintenance hemodialysis (HD). Evidence of cardiac hypofunction was provided by reduced left ventricular ejection fraction (LVEF), enlarged cardiac shadow, severe IDH, and difficulty in fluid removal. The objective of this study was to determine the clinical effects of I-HDF in these patients.

Participants

Participants were 5 patients on maintenance HD who had cardiac hypofunction, which was demonstrated by LVEF 30.5% (SD 4.2%). Mean age was 70.30 years (SD 5.0 years) and mean duration of HD was 17.8 years (SD 15.5 years). The underlying disease was chronic glomerulonephritis in 2 patients, diabetic nephropathy in 2 patients, and IgA nephropathy in 1 patient. All were receiving vasopressors. Two patients had previously undergone coronary artery bypass grafting, 2 had undergone percutaneous coronary intervention, and 1 subject had undergone aortic valve replacement. Mean blood pressure was 80.4 mm Hg (SD 7.2 mm Hg) and the rate of body weight gain was 4.9% (SD 0.7) over a 2-day interval.

Methods

HD was performed for a period of 6 months and was then followed by I-HDF for 6 months. Treatment conditions for both HD and I-HDF were as follows: blood flow rate 224.0 mL/min (SD 41.6 mL/min), dialysate flow rate 500 mL/min, and duration per session 4.1 h (SD 0.2 h). HD was performed with the following HD filters: BP-N130[®] (JMS Co., Ltd., Tokyo, Japan), VPS-15HA[®] (Asahi Kasei Medical Co., Ltd., Tokyo, Japan), NV-21X[®] (Toray Medical Co., Ltd., Tokyo, Japan), and PES-25Dα[®] (Nipro Corporation, Tokyo, Japan). The following I-HDF filters were used: TDF-15H[®] (Toray Medical), ABH-21P[®] (Asahi Kasei Medical), and FIX-250Seco[®] (Nipro Corporation). During each I-HDF session, 200 mL of back-filtered dialysate was infused at a rate of 150 mL/min every 30 min with the GC-110N[®] HD alarm system (JMS Co.) and CarboStar P[®] dialysate (Yoshindo Co., Ltd., Toyama, Japan).

The end points were DW, cardiothoracic ratio (CTR), serum albumin (ALB), normalized protein catabolism rate (nPCR), and percentage creatinine generation rate, which we compared between HD and I-HDF. Blood was sampled every 4 weeks during each of the 6-month periods in which HD and I-HDF were performed. Echocardiography was performed at the end of each period. Echocardiographic end points were LVEF, fractional shortening (FS), left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left atrial diameter, which were compared between HD and I-HDF.

To calculate the mean plasma refilling rate (PRR) over a 30-min interval in 3 patients, the rate of change in circulating blood volume (%ΔBV) was used, which was measured using the CRIT-LINE Monitor[®] (JMS Co.). A comparative analysis was then performed.

To evaluate the microcirculation, a Pocket LDF[®] laser blood flowmeter (JMS Co.) was attached to the earlobe on the side contralateral to the limb used for the dialysis shunt in 4 patients so as to calculate the mean fluctuation in pulse amplitude in 1 min, and then changes in blood flow were investigated. In addition, changes in tissue blood flow were determined during HD and I-HDF and compared, with 5 min after the start of the procedure as a standard assessment period. The blood flow index (BFI) and stability index (SI) obtained from Pocket LDF[®] data were also used to evaluate blood flow stability. When arteriosclerosis progresses, the range of oscillation in the blood flow waveform usually changes due to decreased vasodilation, occlusion, or stenosis. BFI is an index that captures only the oscillatory component of blood flow, which is independent of the volume of blood flow and serves to evaluate impaired organ-specific blood flow that is independent of hemodynamics. In addition, the SI is the coefficient of variation obtained by dividing SD by the mean and is an index of the degree of stability of flow motion.

All results are shown as mean values (SD). Statistical analysis was performed using the paired *t* test, and a hazard ratio of <5% was considered to indicate a significant difference.

Results

Dry Weight and Cardiothoracic Ratio

Mean DW was 62.6 kg (SD 11.2) during the HD period and was significantly lower during the I-HDF period at 59.7 kg (SD 11.5; *p* < 0.01). Mean CTR was 59.0% (SD 2.7) during the HD period and was significantly lower during the I-HDF period at 56.7% (SD 2.7; *p* < 0.01).

Cardiac Function Evaluation (Echocardiography)

No significant differences were observed in either LVEF or FS during the 2 treatment periods, although the values tended to be higher during the I-HDF period. Specifically, LVEF was 30.5% (SD 4.2) during the HD period and 37.7% (SD 13.7) during the I-HDF period, while FS was 15.2% (SD 1.5) and 18.8% (SD 7.9), respectively. Left ventricular end-diastolic diameter was 62.7 mm (SD 7.5) during the HD period and 59.1 mm (SD 8.7) during the I-HDF period, with no significant differences between the 2 treatment periods, although the values tended to improve during the I-HDF period. Left ventricular end-systolic diameter was 53.2 mm (SD 6.9) during the HD period and was significantly higher during the I-HDF period at 48.1 mm (SD 8.9; *p* < 0.05), and left atrial diameter was 48.7 mm (SD 8.3) and 43.0 mm (SD 3.0), respectively. No significant differences were observed between the 2 treatment periods, although the values tended to improve during the I-HDF period (Fig. 1).

Fig. 1. Comparison of cardiac function (echocardiogram) between HD and I-HDF. * $p < 0.05$. LVEF, left ventricular ejection fraction; FS, fractional shortening; LAD, left atrial diameter; HD, hemodialysis; I-HDF, infusion hemodiafiltration; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; ns, non significant.

Fig. 2. Comparison of PRR between HD and I-HDF ($n = 3$). PRR, plasma refilling rate; HD, hemodialysis; I-HDF, infusion hemodiafiltration.

Nutritional Indices

No significant differences were observed in either ALB or nPCR during the 2 treatment periods, although the values tended to be higher during the I-HDF period. Specifically, ALB was 3.4 g/dL (SD 0.2) during the HD period and 3.4 g/dL (SD 0.3) during the I-HDF period, while nPCR was 0.82 g/kg/day (SD 0.10) and 0.84 g/kg/day (SD 0.10), respectively. Percentage creatinine generation rate was 80.5% (SD 17.6) during the HD period and was significantly lower during the I-HDF period at 83.7% (SD 17.6; $p < 0.01$).

PRR Study (3 Patients)

A nonsignificant decrease in PRR was observed over time during the HD period. During the I-HDF period, a nonsignificant increase in PRR was observed during the latter half of treatment and particularly after 150 min of treatment (Fig. 2).

Evaluation of Microcirculation (4 Patients)

There was a transient increase in tissue blood flow during intermittent infusion in the I-HDF period (Fig. 3). In addition, comparing the relative changes in tissue blood flow during the HD and I-HDF periods revealed a nonsignificant decrease in tissue blood flow volume during the latter part of treatment due to peripheral circulatory failure associated with fluid removal in the HD period. However, the tissue blood flow volume remained stable from the start till the end of treatment during the I-HDF period, and a nonsignificant increase in blood flow was observed during treatment, particularly after 150 min (Fig. 4). BFI was 76.0% (SD 27.2) during the HD period and was significantly lower during the I-HDF period at 39.1% (SD 15.5; $p < 0.05$). Similarly, SI was 0.44 (SD 0.23) during the HD period and was significantly lower during the I-HDF period at 0.38 (SD 0.01; $p < 0.01$).

Discussion

The main cause of decreased circulating blood volume due to fluid removal in patients with IDH is the failure of compensatory mechanisms such as plasma refilling, neuroendocrine responses, and cardiovascular reserve [1],

Fig. 3. Chronological changes in tissue blood flow (earlobe) during I-HDF treatment.

Fig. 4. Relative changes in tissue blood flow for HD vs. I-HDF ($n = 4$). HD, hemodialysis; I-HDF, infusion hemodiafiltration.

although adenosine, which is produced by ischemic organs, is also believed to be a contributing factor [2].

Fluid removal progresses and large amounts of adenosine triphosphate (ATP) are produced during HD, and highly metabolically active organs develop ischemia. When the oxygen supply to these organs decreases, ATP synthesis is impaired, resulting in the production of large amounts of adenosine due to hydrolysis of ATP. However, adenosine causes arteriolar dilation, so when highly metabolically active organs develop ischemia and large amounts of adenosine are produced, the arterioles in these organs dilate, causing increased pressure in the capillaries and venules downstream of these arterioles. Under these conditions, the venular compliance in these highly metabolically active organs in the gastrointestinal

system is increased, so the capacity increases significantly as the pressure in these venules increases. This is known as the De Jager-Krogh phenomenon [3]. In other words, ischemia in the viscera results in accumulation and increased blood volume in these organs. Furthermore, water is pushed out of the capillaries in organs with dilated venules into the extravascular space as the pressure increases. As a result, the venous return volume to the heart rapidly decreases, which in turn causes decreased cardiac output and results in rapid hypotension.

During this study, organ ischemia could be prevented and the De Jager-Krogh phenomenon was suppressed by performing intermittent infusion during I-HDF, and this may have facilitated plasma refilling during the latter half of treatment. Furthermore, BFI and SI were lower and more stable during I-HDF than during HD, suggesting that I-HDF stabilizes hemodynamics.

Eguchi et al. [4] were unable to confirm whether actual increases in tissue blood flow occurred in association with increased $\% \Delta BV$ during simultaneous intermittent infusion in cases complicated by arteriosclerosis obliterans, cases complicated by severe cardiac disease, and cases of advanced arteriosclerosis. They were also unable to confirm improvement of the clear space and postulated that I-HDF was not expected to be effective in these cases. In the present study, I-HDF was performed in patients with cardiac hypofunction on maintenance HD and it was confirmed that increases in tissue blood flow were associated with increases in the $\% \Delta BV$ that occurred during intermittent infusion. These findings suggest that, to some extent, I-HDF contributed to stabilizing hemodynamics and improving cardiac function in these patients.

Conclusion

Excess fluid is one cause of heart failure symptoms. I-HDF facilitates the removal of excess fluid from the body and may contribute to improved cardiac function.

Acknowledgment

None.

Statement of Ethics

The study was reviewed and approved by the Medical Ethics Committee at the Public Tomioka General Hospital. Written informed consent was obtained from the study participants, including consent to participate and to publish the findings.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.S. designed the study and wrote the initial draft of the manuscript. M.M. contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation and critically reviewed the manuscript. All authors have approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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