In vitro Evaluation of Solute Removal Characteristics in Intermittent Infusion Hemodiafiltration

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Keywords

Intermittent infusion hemodiafiltration · Solute removal characteristics · Time-averaged solute clearance · Infusion flow rate · Hemodiafiltration

Abstract

Background: In a typical hemodialysis (HD) session, excessive water removal sometimes induces peripheral circulatory failure and a rapid drop in blood pressure. Intermittent infusion hemodiafiltration (I-HDF), a new modality of dialysis therapy, has been developed to improve peripheral circulation by repeated intermittent infusion of dialysate during an HD session. In a typical I-HDF session, we infuse a volume of 200 mL of ultrapure dialysate by backfiltration at 150 mL/min every 30 min. The same volume is alternately removed from the patient's blood by filtration at a constant rate after each infusion. However, solute removal characteristics in I-HDF have not been clarified previously. We therefore conducted an in vitro study to investigate the characteristics of solute removal and the factors affecting such removal. **Summary:** We used human plasma to evaluate the effects of filtration (QF)/infusion (QI) flow rates on solute clearance (CL) and to estimate the time-averaged solute CL (TACL) values. The CL values for all solutes decreased with increasing QI. For small molecules such as urea, the CL val-

ues predominantly decreased with increasing QI because of decreasing diffusive transport. For medium and large solutes such as β_2 microglobulin or larger, CL values predominantly increased with increasing QF because of increasing convective transport. However, the effects of these changes on TACL values were small compared with the CL value in a typical HD session because of the alternate filtration and infusion in I-HDF. **Key Messages:** Solute removal characteristics in I-HDF do not differ significantly from those in conventional HD treatment.

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Introduction

Dialysis patients frequently develop hypotension and peripheral circulatory failure during dialysis. Intermittent infusion hemodiafiltration (I-HDF) was developed to resolve these issues [1]. I-HDF is a treatment modality that involves intermittent infusion of supplementary fluid during normal hemodialysis (HD), and the combined volume of net fluid removal and supplementary fluid undergoes ultrafiltration within a single session. Intermittent infusion is expected to maintain blood pressure and improves peripheral circulation. The infusion settings during I-HDF are the treatment time (T [min]), infusion flow

rate (Q_{if} [mL/min]), single infusion volume (V_{if} [mL]), number of infusions per session (T_i [times/session]), and number of infusion cycles (ΔT [min]). Using these parameters, the following parameters can be derived: $T_i = T/\Delta T$, total infusion volume = $V_{if} \times T_i$, infusion time (t_{IF}) = $V_{if}/Q_{if} \times T_i$, and filtration time (t_F) = $T - t_{IF}$.

Typical conditions of I-HDF are $Q_{if} = 150$ mL/min, $V_{if} = 200$ mL, $\Delta T = 30$ min, and $T_i = 7$ times (no infusion at the end of the session). Usually, the supplementary fluid is infused by means of backfiltration into the blood through the dialyzer membrane, although some machines infuse the fluid directly into the blood circuit.

Backfiltration occurs via convection from outside the capillary to the inside, while normal filtration removes fluid from inside the capillary to the outside. In I-HDF, fluid supplementation takes place by means of backfiltration during the infusion phase. During this process, because solute transfer occurs as a result of backfiltration, the amount of solute transferred by diffusion, which is driven by the solute concentration gradient, can decrease in I-HDF. We speculated that the time-average clearance (TACL) for the entire session of I-HDF is different from that in HD. However, few reports have determined TACL during I-HDF.

Objective

The objective of this study was to clarify how TACL values change with variations in the operating conditions such as Q_{if} , V_{if} , and T_i .

Materials and Methods

CL values during backfiltration and forward filtration were determined by in vitro experiments, and the TACL of the entire session of IHDF was estimated based on these in vitro results as follows:

$$\text{I-HDF TACL} = \frac{(\text{backfiltration CL} \times t_{IF} + \text{forward filtration CL} \times t_F)/T}{(1)} \quad (1)$$

Thereafter, the results were used to estimate TACL values during 1 session ($T = 240$ min) under different operating conditions, and then comparative investigations between these different conditions were carried out.

Changes in CL Value When Q_f Was Changed from Forward Filtration to Backfiltration

We performed in vitro experiments using human plasma obtained as the effluent of plasma exchange in order to investigate the CL value when Q_f was changed from forward filtration to backfiltration. This study was approved by the Tokyo Women's Medical University Ethics Committee.

The plasma exchange effluent was circulated within the blood side of the IHDF circuit at a flow rate (Q_p) of 200 mL/min, while the dialysate flow rate (Q_d) was set to 500 mL/min. We used Q_f values of -200 , -150 , -100 , -50 , 0 , 15 , and 50 mL/min. The negative ($-$) values of Q_f value indicate backfiltration; positive ($+$) values indicate forward filtration. After setting the various flow rates, these were kept constant for 150 s or more. We then measured the concentrations of solutes at the inlet (CPI) and the outlet (CPO) of blood side of the dialyzer, as well as the outflow concentration in the dialysate side (CDO) of the dialyzer. We used the MFX-15Seco hemodiafilter (polyethersulfone, area 1.5 m²; Nipro Corp., Osaka, Japan) after circulating the plasma for 30 min. The experiment was performed in a single pass.

The solutes we measured and used as indices were urea, creatinine (Cr), inorganic phosphate (P), uric acid (UA), β_2 microglobulin (β_2 -MG), and α_1 -MG.

The CL value was calculated using the following formula:

$$CL = (CPI - CPO)/CPI \times Q_p \quad (2)$$

Calculating TACL during I-HDF

Based on the in vitro experiments using the abovementioned solutes, the changes in CL from positive filtration to backfiltration in relation to changes in the Q_f value for each solute were approximated using a quadratic equation, and the estimation formula for CL in terms of Q_f was derived.

Analysis Based on the Model

TACL during I-HDF was determined by Q_{if} , V_{if} , and T_i . We determined the TACL for urea and β_2 -MG during HD and I-HDF under various set infusion conditions. The operating conditions were as follows: Q_{if} was set to -100 , -150 , or -200 mL; V_{if} was between 0 and 200 mL; and T_i was between 2 and 32 times.

Results

Changes in CL Values When Q_f Changed from Forward Filtration to Backfiltration

Figure 1 shows the results for the CL value for each Q_f during the in vitro experiment. When Q_f was reduced, CL values for all solutes decreased, and the lowest Q_f value during this experiment (-200 mL/min) also yielded the lowest CL values. The CL values for urea, Cr, P, and UA plateaued as Q_f values increased; no such association was observed for β_2 -MG and α_1 -MG, for which CLs continued to increase as the Q_f values increased.

Estimation Formula for the CL Value for Each Solute in Terms of Q_f

The following estimation formulas were obtained for the CL values for each solute using the above results.

$$\text{Urea: } -4.95 \times 10^{-4} Q_f^2 + 1.06 \times 10^{-1} Q_f + 192.06 \text{ mL/min} \quad (3) \\ R^2 = 0.999$$

Fig. 1. Changes in CL values in relation to Qf value changes. CL, clearance; β 2-MG, β 2 microglobulin; UA, uric acid; Cr, creatinine.

$$P: -3.54 \times 10^{-4} Q_f^2 + 2.31 \times 10^{-1} Q_f + 176.50 \text{ mL/min} \quad (4)$$

$$R^2 = 0.978$$

$$Cr: -2.83 \times 10^{-4} Q_f^2 + 1.95 \times 10^{-1} Q_f + 181.51 \text{ mL/min} \quad (5)$$

$$R^2 = 0.999$$

$$UA: -4.40 \times 10^{-4} Q_f^2 + 2.17 \times 10^{-1} Q_f + 173.62 \text{ mL/min} \quad (6)$$

$$R^2 = 0.989$$

$$\beta 2\text{-MG}: 6.21 \times 10^{-4} Q_f^2 + 3.93 \times 10^{-1} Q_f + 62.70 \text{ mL/min} \quad (7)$$

$$R^2 = 0.9972$$

$$\alpha 1\text{-MG}: 2.91 \times 10^{-4} Q_f^2 + 1.50 \times 10^{-1} Q_f + 1.87 \text{ mL/min} \quad (8)$$

$$R^2 = 0.972$$

Analysis Based on the Model

We compared TACL values for both urea and β 2-MG during HD and I-HDF using equation (3) for urea and equation (7) for β 2-MG. During HD, the CL values for urea and β 2-MG were 192.15 and 62.83 mL/min, respectively; during I-HDF, these values were 191.69 and 63.20 mL/min, respectively. Compared with HD, the TACL value for urea, which is a small molecule, decreased during I-HDF, while the value for β 2-MG, which is relatively large molecule, increased. However, the difference was minor, and we believe there would be no clinically significant difference in TACL if I-HDF were performed under the usual conditions for HD.

Changes in the CL Value When Qf and Vif Were Changed

The following values were set: $Q_p = 200$ mL/min, $Q_d = 500$ mL/min, $\Delta T = 30$ min, and $T = 240$ min. Figure 2 shows the results of the calculated changes in TACL for urea and β 2-MG when Qf and Vif were changed.

The CL value for urea decreased as the total infusion volume increased. This decrease became more conspicuous as the Qif value increased. The CL value for β 2-MG decreased at low Qif values as the total infusion volume increased and increased at high Qif values. This increase in CL values became more conspicuous as the Qif value increased.

Infusion Conditions for TACL During I-HDF

Figures 3 and 4 show the calculated CL values for urea and β 2-MG, respectively, when the Q_p value was set to 200 mL/min, Qif was set to 100, 150, or 200 mL/min, and Vif and Ti ranged between 50 and 300 mL and 2 and 32 times, respectively. CL values for urea decreased as either Vif or Ti values increased, and this trend became more pronounced as Qif values increased. CL values for β 2-MG increased as Vif or Ti values increased, while the increase was subtle and the change became prominent when both Vif and Ti increased simultaneously. Also, this trend became more pronounced as Qif values increased. The CL values for urea and β 2-MG changed from 192.2 and 62.8 mL/min under the condition of ordinary HD (where Qif = 0) to 187.1 and 68.9 mL/min under the conditions of IHDF with Qf = 200 mL/min, Vif = 300 mL, Ti = 32 times, and these conditions had the maximum value for each index.

Discussion

Based on the results of the in vitro experiments and the TACL values calculated using the CL estimation formulas obtained from these experiments, there are clearly no major differences between TACL values obtained for HD and I-HDF even with various I-HDF infusion conditions. Also, CL values for urea and β 2-MG were changed by the different settings for Qif, Vif, and Ti, which are the operating conditions for I-HDF. Specifically, when Qif, Vif, and Ti values increased, TACL values for urea decreased while those for β 2-MG increased.

Urea CL in I-HDF was not greater than that in HD under any conditions of filtration or infusion during the I-HDF session, although the differences were minimal. We believe this is because the magnitude of the increased urea CL value during forward filtration is smaller than that of the decreased urea CL value during backfiltration, and therefore the former cannot offset the latter even when increasing Vif or Ti. Meanwhile, the degree of the increase in CL value for β 2-MG during forward filtration was greater than that of the decrease in CL value during backfiltration, so the increase in Qif, Vif, or Ti resulted in

Fig. 2. Changes in time-averaged CL during I-HDF in relation to Qif and total infusion volume. CL, clearance; β 2-MG, β 2 microglobulin.

Fig. 3. Changes in time-averaged CL during I-HDF in relation to the Vif and Vt values for each Qif (urea). CL, clearance.

Fig. 4. Changes in time-averaged CL during I-HDF in relation to the Vif and Tt values for each Qif (β 2-MG). β 2-MG, β 2 microglobulin.

a larger TACL value. These differences between urea CL and β 2-MG CL are derived from differences in the slope of the curves of the CL estimation formulas with respect to the Qf values shown in Figure 1.

I-HDF decreases CL for low molecular weight solutes and increases that of solutes with higher molecular weight, compared with CL values in HD. Under the highest infusion conditions tested ($Q_{if} = 200$ mL/min, $V_{if} = 300$ mL, $T_i = 32$ times), the urea CL was 2.7% smaller and the β 2-MG CL value was 9.7% larger than the values obtained by HD. I-HDF is useful when the elimination of β 2-MG should be increased, even though such increase is minimal. Also, we believe that the increase in Q_{if} , V_{if} , or T_i can increase the TACL of substances for which the CL during forward filtration increased more than the decrease in CL during backfiltration, such as α 1-MG. Mine-shima et al. reported that clear space values increased in all substances irrespective of their molecular weight in I-HDF compared with HD in a clinical study conducted with 17 patients. Among them, the increase was significantly larger for α 1-MG compared with other substances [2]. α 1-MG has a higher molecular weight than β 2-MG and its CL is increased more by forward filtration. The volume of forward filtration is larger in I-HDF than HD due to the volume of infusion, which affects the differences in CL values and clear space values of α 1-MG and β 2-MG. Moreover, the CL of α 1-MG by diffusion is small and is not mitigated by backfiltration. This is another reason why the TACL of α 1-MG is larger in I-HDF than in

HD. Furthermore, clear space increased for low molecular weight substances, although the TACL values decreased. I-HDF serves to improve peripheral perfusion and to enhance the transport of water and solutes from the extravascular to intravascular space by virtue of intermittent infusion. We believe that the increased clear space for these low molecular weight solutes might be due to the fact that the elimination of small solutes become more homogeneous in the body, which provides evidence that I-HDF improves peripheral circulation.

During this study, we did not consider possible improvement in membrane permeability due to nonstationary effects or membrane cleansing effects caused by switching alternately between backfiltration and forward filtration. Also, all dialysis machines with the I-HDF mode automatically decrease the QB during replacement via backfiltration in order to minimize the increase in venous pressure. We expect that TACL during I-HDF would be even lower in actual clinical settings.

Conclusion

The CL value decreased during backfiltration, and this decrease was more conspicuous for high molecular weight substances. No major differences were observed between TACL in the normal operating conditions of I-HDF and HD with the same QB and QD. The in vitro experiments and mathematical modeling revealed that the CL for low

molecular weight substances decreased, while the CL for β 2-MG or for substances with larger molecular weight increased when Qif, Vif, or Ti were increased.

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Statement of Ethics

This study was approved by the Tokyo Women's Medical University Ethics Committee, and informed consent was obtained from all participants.

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Disclosure Statement

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Author Contributions

T.A., M.M., and I.I.: study concept and design; T.A., I.I., and J.M.: analysis and interpretation of data; T.A., N.H., I.I., and J.M.: drafting of the manuscript; K.T. and K.N.: revision of the manuscript for important intellectual content.