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ORIGINAL ARTICLE

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Differences in cerebral and hepatic oxygenation in response to intradialytic blood transfusion in patients undergoing hemodialysis

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Abstract

Hemodialysis (HD) patients frequently experience severe anemia, requiring intradialytic blood transfusion. Severe anemia leads to deterioration of systemic tissue oxygenation. However, few reports have examined the effect of intradialytic blood transfusion on tissue oxygenation changes. This study aimed to (i) monitor the differences in tissue oxygenation in the brain and liver during intradialytic blood transfusion, and (ii) elucidate the clinical factors affecting cerebral and hepatic oxygenation. Thirty-eight HD patients with severe anemia requiring intradialytic blood transfusion were included (27 men, 11 women; mean age, 70.2 ± 1.6 years). Cerebral and hepatic regional oxygen saturation (rSO_2) values were monitored using near-infrared spectroscopy (INVOS 5100c oxygen saturation monitor). Cerebral and hepatic rSO_2 were significantly higher after than before blood transfusion ($p < 0.001$, both). Furthermore, hepatic rSO_2 was significantly higher than cerebral rSO_2 after transfusion ($p = 0.004$). In multivariable linear regression analysis, cerebral rSO_2 changes were independently associated with the natural logarithm of hemoglobin (Hb) ratio (Hb after/before transfusion) (standardized coefficient: 0.367, $p = 0.023$), whereas hepatic rSO_2 changes were independently associated with the natural logarithm of [Hb ratio/colloid osmotic pressure ratio (colloid osmotic pressure after/before transfusion)] (standardized coefficient: 0.378, $p = 0.019$). In conclusion, throughout intradialytic blood transfusion, brain and liver tissue oxygenation improved. Hepatic rSO_2 was significantly higher than cerebral rSO_2 at the end of HD. Furthermore, cerebral oxygenation changes were associated with only transfusion-induced Hb increase, whereas hepatic oxygenation changes were associated with both transfusion-induced Hb increase (positive changes) and ultrafiltration-induced colloid osmotic pressure increase (negative changes).

Keywords Blood transfusion · Brain · Hemodialysis · Liver · Oxygenation

Introduction

In dialysis therapy, erythropoiesis-stimulating agents dramatically improve the hemoglobin (Hb) levels in patients undergoing hemodialysis (HD), thereby decreasing the need for blood transfusion [1, 2]. Nevertheless, HD patients frequently experience severe anemia that requires intradialytic blood transfusion to improve Hb levels. Recently, splanchnic ischemia including non-occlusive mesenteric ischemia (NOMI) has received close attention as one of the major and lethal complications in patients undergoing HD [3–5], and blood transfusion itself was reported to be associated with the occurrence of NOMI in postoperative patients [6, 7]. In the clinical setting, cerebral regional oxygen saturation

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(rSO_2), a real-time marker of tissue oxygenation measured using near-infrared spectroscopy [8–11], has been shown to significantly increase in response to Hb increases associated with intradialytic blood transfusion [12]. Moreover, splanchnic rSO_2 has been reported to show larger variability than that in cerebral rSO_2 during blood transfusion in neonates with transfusion-related acute gut injury [13]. Therefore, it may be suspected that intradialytic blood transfusion directly influences the splanchnic tissue oxygenation, including liver tissue oxygenation, in addition to the cerebral oxygenation. However, to date, few reports have examined the association between intradialytic blood transfusion and changes in tissue oxygenation. Furthermore, data are lacking regarding the changes in tissue oxygenation caused by intradialytic blood transfusion in each organ, including the brain and splanchnic organs. Therefore, this study aimed to (i) monitor the differences in tissue rSO_2 changes in the brain and liver during intradialytic blood transfusion, and (ii) elucidate the clinical factors affecting the changes in cerebral rSO_2 and hepatic rSO_2 during HD with intradialytic blood transfusion.

Materials and methods

Patients

In this single-center observational study, we included patients with severe anemia undergoing HD who met the following criteria: (i) end-stage renal disease managed with intermittent HD; (ii) severe anemia requiring blood transfusion that was caused by hemorrhagic disorder including gastrointestinal bleeding, surgery-related anemia, or renal anemia; and (iii) previous intradialytic blood transfusion to improve severe anemia as decided by a medical practitioner. The exclusion criteria were (i) coexisting major disease including congestive heart failure and apparent neurological disorders or a history of cerebrovascular disease, and (ii) tissue thickness > 20 mm from the skin to the surface of the liver in the right intercostal area as measured on ultrasonography.

Forty-three patients met the inclusion criteria and were enrolled in the study. However, five patients were excluded from the analysis because of missing data. Therefore, 38 patients were finally included in this study (27 men, 11 women; mean age, 70.2 ± 1.6 years; mean HD duration, 2.9 ± 0.9 years; Table 1). Each patient underwent HD 2 or 3 times per week for 3–4 h each. The causes of chronic renal failure included type 2 diabetes mellitus (12 patients), nephrosclerosis (10 patients), chronic glomerulonephritis (7 patients), and others (9 patients). The causes of severe anemia were gastrointestinal bleeding (12 patients), renal anemia (12 patients), inflammation-related anemia (7 patients), operation-related anemia (3 patients), and other hemorrhagic disorders (4 patients). Blood transfusion was performed at a rate of 200 mL/h, with a total volume of 376 ± 22 mL. A native arterio-venous fistula was used as vascular access in all patients.

Table 1 Patients' general characteristics

Number of patients	38
Women/men	11/27
Age (years)	70.2 ± 1.6
HD duration (years)	2.9 ± 0.9
HD time (hours)	3.6 ± 0.1
Disease	
Diabetes mellitus, *n*	12
Nephrosclerosis, *n*	10
Chronic glomerulonephritis, *n*	7
Other, *n*	9
Comorbidities	
Cardiovascular disease, *n* (%)	16 (42.1)
Causes of anemia	
Gastrointestinal bleeding, *n* (%)	12 (31.6)
Renal anemia, *n* (%)	12 (31.6)
Inflammation-related anemia, *n* (%)	7 (18.4)
Operation-related anemia, *n* (%)	3 (7.9)
Other hemorrhagic disorders, *n* (%)	4 (10.5)
Blood transfusion volume (mL)	376 ± 22
DW-adjusted blood transfusion volume (mL/kg-DW)	6.8 ± 0.4
Fluid removal (L/session)	1158 ± 136
Ultrafiltration rate (mL/h)	320 ± 37
Medication, *n* (%)	
Renin–angiotensin system blocker	10 (26.3)
Calcium channel blocker	18 (47.4)
Beta blocker	19 (50.0)
Vitamin D analog	10 (26.3)
Statin	12 (31.6)
Antiplatelet agents	19 (50.0)
Erythropoiesis-stimulating agent	30 (78.9)
Vasopressor use during HD	6 (15.8)

Values are shown as mean ± standard error unless indicated otherwise
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Ethical approval

All participants provided written informed consent to participate. The study was approved by the Institutional Review Board of Saitama Medical Center, Jichi Medical University, Japan (RIN 15-104) and conformed to the provisions of the Declaration of Helsinki (as revised in Tokyo in 2004).

Patients' baseline characteristics and clinical laboratory measurements

We collected the patients' baseline characteristics and other relevant data from their medical charts. The primary disease

underlying the dialysis requirement and the coexistence of cardiovascular disease were extracted from the medical records. The causes of anemia were confirmed from the medical records and the attending doctors.

Blood pressure and heart rate were measured with the patients in the supine position before and after the HD sessions, while the intradialytic blood transfusion volume was confirmed in each HD patient with severe anemia. Blood samples were obtained at an ambient temperature from the arteriovenous fistula of each patient before the intradialytic blood transfusion and after the HD.

Monitoring of tissue oxygenation before and after HD

Tissue rSO_2, a marker of tissue oxygenation in the brain and liver, was monitored using an INVOS 5100c saturation monitor (Covidien Japan, Tokyo, Japan). This instrument uses a light-emitting diode that transmits near-infrared light at two wavelengths (735 and 810 nm) and two silicon photodiodes that act as light detectors to measure oxygenated Hb and deoxygenated Hb. The ratio of O_2 Hb to total Hb (oxygenated Hb + deoxygenated Hb) signal strength, the corresponding percentage, is read as a single numerical value that represents the rSO_2 [14, 15]. All data obtained by this instrument were immediately and automatically stored in sequence. The inter-observer variance of this instrument (i.e., the reproducibility of the rSO_2 measurement) is acceptable, as previously reported [16–18]. Therefore, rSO_2 is considered reliable for estimating actual cerebral oxygenation levels. Furthermore, the light paths leading from the emitter to the different detectors share a common part: the 30-mm detector assesses superficial tissue, while the 40-mm detector is used to assess deep tissue. By analyzing the differential signals collected by the different detectors, the current data for rSO_2 and total Hb signal strength values were supposed to be obtained in deep tissue at 20–30 mm from the body surface [19, 20]. These measurements were performed at 6-s intervals. We evaluated the mean rSO_2 in each compartment for 5 min as a single rSO_2 value.

At the initiation of intradialytic blood transfusion and the end of HD, sensors were attached to the patient's forehead and right intercostal area above the liver for the measurement of rSO_2 during HD. The right intercostal area just above the liver was identified using ultrasonography before transfusion. During HD, each patient was instructed to lie quietly in bed and refrain from eating.

Calculation of changes in clinical parameters before intradialytic blood transfusion and at the end of HD

To evaluate the influences of clinical parameters on the changes in cerebral and hepatic rSO_2 in this study, we calculated the change in each clinical parameter between before HD and at the end of HD, or before intradialytic blood transfusion and at the end (Table 2). In particular, the Hb ratio was calculated as the ratio of Hb level at the end of HD and that before intradialytic blood transfusion. With respect to the blood transfusion volume, to correct for the body weight difference among the patients, we calculated the dry weight-adjusted blood transfusion volume [intradialytic blood transfusion volume (mL)/dry weight (kg)]. Furthermore, throughout the ultrafiltration during HD, intravascular colloid osmotic pressure (COP) is important to maintain the systemic tissue microcirculation and usually increases owing to the increase in total protein and albumin concentrations in response to the decrease of circulating plasma volume [21]. To examine the influence of COP on the changes in cerebral and hepatic rSO_2, the COP before intradialytic blood transfusion and that at the end of HD were calculated using the equation below (a specialized method for HD patients)

Table 2 Changes in hemodynamic parameters during HD and laboratory findings before and after intradialytic blood transfusion

Hemodynamic parameters	Before HD	After HD	*p*
Body weight (kg)	58.5 ± 1.8	57.3 ± 1.8	< 0.001
Systolic blood pressure (mmHg)	132 ± 4	150 ± 4	0.001
Diastolic blood pressure (mmHg)	69 ± 2	76 ± 2	0.005
Heart rate (/min)	81 ± 2	82 ± 2	0.758
Laboratory findings	Before blood transfusion	After HD	*p*
Hemoglobin (g/dL)	7.1 ± 0.1	9.0 ± 0.2	< 0.001
Serum albumin (g/dL)	2.6 ± 0.1	2.7 ± 0.1	0.129
Serum sodium (mEq/L)	136.2 ± 0.6	137.7 ± 0.4	0.036
Colloid osmotic pressure (mmHg)	15.2 ± 0.4	16.7 ± 0.5	0.026

Values shown are mean ± standard error

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[21]. Moreover, the COP ratio, which reflects the degree of circulating plasma volume decrease induced by ultrafiltration during HD, was also calculated as the ratio of the COP level at the end of HD and that before intradialytic blood transfusion.

$$\begin{aligned}\text{COP (mmHg)} = &-7.91 + 5.64 \times \text{serum albumin (g/dL)} \\ &+ 3.00 \times \left[\text{total protein (g/dL)}\right. \\ &\left. - \text{serum albumin (g/dL)}\right]\end{aligned}$$

In addition, to simultaneously evaluate the Hb increase induced by transfusion and the COP increase by ultrafiltration and their influence on tissue rSO_2 changes, we also calculated the Hb ratio/COP ratio in each patient as one of the clinical parameters in this study.

Statistics

Data are expressed as mean ± standard error. The changes in Hb level before versus after intradialytic blood transfusion, Hb ratio, dry weight-adjusted blood transfusion volume, and Hb ratio/COP ratio were not normally distributed; therefore, these variables were transformed using the natural logarithm (Ln). The differences in tissue rSO_2 before intradialytic blood transfusion and after HD in the brain and liver were evaluated using Student's *t* test for paired or non-paired values. Variables that were significantly correlated with changes in tissue rSO_2 before and after intradialytic blood transfusion in each organ in a simple linear regression analysis were included in the multivariable linear regression analysis, to identify factors affecting the increase in cerebral or hepatic rSO_2 induced by intradialytic blood transfusion. All analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM, Armonk, NY, USA). Differences of $p < 0.05$ were considered statistically significant.

Results

As shown in Table 2, there were significant increases in systolic and diastolic blood pressure, Hb, serum sodium concentration, and COP, in addition to a significant decrease in body weight.

The cerebral and hepatic rSO_2 values at the end of HD significantly increased compared with those before the intradialytic blood transfusion (cerebral rSO_2, 43.8 ± 1.5% vs. 48.0 ± 1.4%, hepatic rSO_2, 46.7 ± 1.7% vs. 55.4 ± 2.0%; $p < 0.001$, both; Fig. 1). Furthermore, the hepatic rSO_2 was significantly higher than the cerebral rSO_2 at the end of HD ($p = 0.004$), although there was a no significant difference between cerebral and hepatic rSO_2 before the intradialytic blood transfusion ($p = 0.200$; Fig. 1).

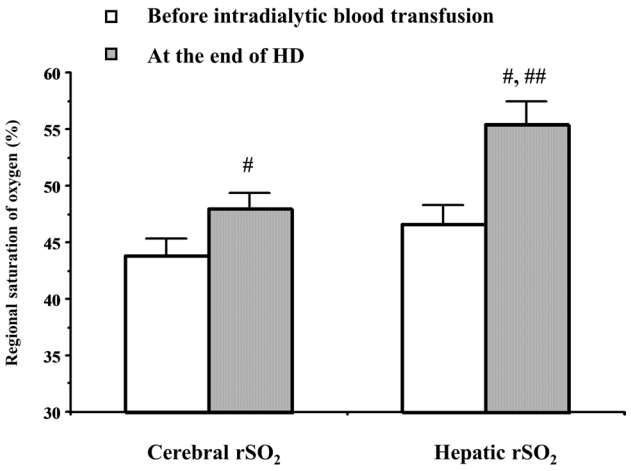

Fig. 1 Comparison of cerebral and hepatic rSO_2 between before intradialytic blood transfusion and at the end of HD. #$p < 0.001$ vs. before intradialytic blood transfusion; ##$p = 0.004$ vs. cerebral rSO_2 at the end of HD. *HD* hemodialysis, *rSO_2* regional saturation of oxygen

Next, simple linear regression analyses were performed using variables including changes in hemodynamic parameters before and after HD, as well as Hb, serum albumin, serum sodium, and COP before intradialytic blood transfusion and at the end of HD in association with changes in cerebral or hepatic rSO_2. As shown in Table 3, changes in cerebral rSO_2 showed significantly positive correlations with the Ln of dry weight adjusted blood transfusion volume and the Ln of Hb ratio in a simple linear regression analysis, and the multivariable linear regression analysis showed that changes in cerebral rSO_2 were independently associated with the Ln of Hb ratio (standardized coefficient: 0.367, $p = 0.023$). On the other hand, changes in hepatic rSO_2 showed significantly positive correlations with the Ln of dry weight adjusted blood transfusion volume and the Ln of Hb ratio/COP ratio; however, changes in hepatic rSO_2 were independently associated with the Ln of Hb ratio/COP ratio (standardized coefficient: 0.378; $p = 0.019$) in the multivariable linear regression analysis. Furthermore, we performed a multivariable linear regression analysis including DM status, and the presence of DM was not found to have any significant association with changes in cerebral rSO_2 (standardized coefficient −0.051, $p = 0.751$) or hepatic rSO_2 (standardized coefficient −0.001, $p = 0.952$) in this study.

Discussion

In the present study, we confirmed the significant increases in cerebral and hepatic rSO_2 after intradialytic blood transfusion, and changes in hepatic rSO_2 were significantly larger than those in cerebral rSO_2 during transfusion. Furthermore, changes in cerebral rSO_2 were independently associated with the Ln of Hb ratio before and after transfusion, whereas Ln

Table 3 Changes in cerebral and hepatic rSO_2 and variables included in simple and multivariable linear regression analyses

Variables		Changes in cerebral rSO_2 4.20 ± 0.63%				Changes in hepatic rSO_2 8.64 ± 0.98%			
		Simple linear regression		Multivariable linear regression		Simple linear regression		Multivariable linear regression	
		r	*p* value	Standardized coefficient	*p* value	*r*	*p* value	Standardized coefficient	*p* value
Changes in systolic BP (mmHg)	19 ± 3	0.067	0.691			0.153	0.361		
Changes in diastolic BP (mmHg)	9 ± 2	0.085	0.610			0.129	0.441		
Ln of changes in Hb	0.57 ± 0.08	0.317	0.052			0.151	0.366		
Ln of Hb ratio	0.24 ± 0.02	0.367	0.023*	0.367	0.023*	0.194	0.242		
Ln of DW-adjusted blood transfusion volume	1.84 ± 0.06	0.340	0.038*	0.167	0.438	0.325	0.046*	0.186	0.298
Changes in serum albumin (g/dL)	0.17 ± 0.03	0.166	0.320			−0.102	0.541		
Changes in serum sodium (mEq/L)	1.45 ± 0.35	−0.133	0.426			0.174	0.296		
Changes in COP (mmHg)	1.47 ± 0.26	0.054	0.747			−0.173	0.299		
COP ratio	1.10 ± 0.02	0.085	0.611			−0.171	0.304		
Ln of Hb ratio/COP ratio	0.15 ± 0.02	0.310	0.058			0.378	0.019*	0.378	0.019*

Values shown are mean ± standard error

rSO_2 regional saturation of oxygen, *BP* blood pressure, *Hb* hemoglobin, *Ln* natural logarithm, *DW* dry weight, *COP* colloid osmotic pressure

*Statistically significant

of Hb ratio/COP ratio before and after transfusion was the only factor affecting those in hepatic rSO_2.

Regarding the association between changes in cerebral rSO_2 and those in Hb level induced by intradialytic blood transfusion, our finding of a significant increase in cerebral rSO_2 after intradialytic blood transfusion is consistent with that of previous reports [12, 22, 23]. In addition, changes in cerebral oxygenation were reportedly affected by the weight-matched blood transfusion volume and the increase in hematocrit after transfusion [24]. In this study, the Ln of Hb ratio was the only factor independently and positively associated with changes in cerebral rSO_2 throughout intradialytic blood transfusion, whereas the Ln of dry weight-adjusted blood transfusion volume did not show a significant correlation with these changes in the multivariable linear regression analysis. Tissue rSO_2 measurements using near-infrared spectroscopy typically reflect the oxygen saturation in venous (70–80%), capillary (5%), and arterial blood (20–25%) [25]. In anemic status, cerebral functional oxygen extraction rate increases as a compensation to maintain cerebral oxygen metabolism because of the decrease of oxygen supply to the brain [12, 26, 27]. Furthermore, due to the improvement of oxygen-carrying capacity induced by blood transfusion, cerebral functional oxygen extraction rate significantly decreased after an intradialytic blood transfusion [12]. Therefore, the ratio of O_2 Hb to total Hb signal strength in venous blood increases after blood transfusion as compared to that before blood transfusion, and this increase would be associated with an improvement of tissue rSO_2 values after blood transfusion. Thus, the increase in Hb ratio also led to increased oxygen-carrying capacity to peripheral tissues and organs; therefore, this ratio could be a factor affecting the changes in cerebral rSO_2 through the Hb increase induced by intradialytic blood transfusion.

Recently, several reports have demonstrated the importance of hepatic oxygenation monitoring in patients undergoing HD. First, hepatic rSO_2 was found to be well-maintained during HD with ultrafiltration in stable HD patients [28]. Second, it would be postulated that there might be differences in changes in tissue oxygenation induced by intradialytic blood transfusion in the brain, liver, and lower-leg muscles [29]. Additionally, deterioration of hepatic oxygenation precedes intradialytic hypotension onset during HD; therefore, non-invasive and continuous monitoring of hepatic rSO_2 may be important to predict the onset of intradialytic hypotension [30]. In HD patients, splanchnic ischemia including NOMI was reportedly induced by the intradialytic hypotension and intravascular volume depletion caused by ultrafiltration during HD [4, 31], in addition to the observed association between NOMI and blood transfusion in postoperative patients [6, 7]. Therefore, in this study, we focused on the association between changes in hepatic rSO_2 and those in Hb level by intradialytic blood transfusion and on the influence of ultrafiltration during HD. It was recently reported that hepatic rSO_2 was relatively higher than cerebral rSO_2 in maintenance HD patients with well-maintained Hb levels [28]. However, we found no differences in tissue rSO_2 between the brain and liver under the condition of severe anemia before intradialytic blood transfusion. This result

might imply that hepatic oxygenation tends to decrease rather than cerebral oxygenation in response to the Hb decrease because the regulation of systemic circulation usually prioritizes cerebral blood flow and oxygenation at the expense of blood flow and oxygen supply to other compartments, including the liver [32, 33]. Therefore, concerning the increase in oxygen-carrying capacity accompanied by Hb increase after intradialytic blood transfusion, hepatic oxygenation might be more likely to improve than cerebral oxygenation through the release from compensation of the hepatic circulation, to prevent cerebral circulatory impairments under a severe anemic status. Furthermore, with respect to the result confirming that changes in hepatic rSO_2 were independently associated with Ln of Hb ratio/COP ratio, hepatic rSO_2 might be influenced by two different factors: (i) Hb increase associated with intradialytic blood transfusion (positive influence) and (ii) COP increase induced by ultrafiltration during HD (negative influence). A positive influence of intradialytic blood transfusion to hepatic oxygenation would be via increase of the oxygen-carrying capacity induced by Hb increase, similar to the effect on cerebral oxygenation. In contrast, an increase in COP showed a negative influence on the changes in hepatic rSO_2. In general, the changes in central circulation associated with ultrafiltration during HD are usually evaluated by the changes in relative blood volume using a blood volume monitor [34]. However, these changes cannot reflect the changes in central circulation because of the Hb increase induced by the intradialytic blood transfusion in this study. Therefore, the changes in central circulation associated with ultrafiltration were evaluated by changes in plasma volume before and after intradialytic blood transfusion. Under the assumption that the total amount of serum protein in the central circulation does not change during HD, COP increases via the increase of serum protein concentration in response to a decrease in plasma volume associated with ultrafiltration during HD [35]. Thus, the COP-associated clinical parameters, including changes in COP and COP ratio before and after intradialytic blood transfusion, were evaluated for an association with changes in cerebral or hepatic rSO_2. In this study, the COP ratio reflects the degree of plasma volume decrease induced by ultrafiltration before and after an intradialytic blood transfusion. Recently, hepatosplanchnic blood flow reportedly decreased during HD with ultrafiltration as a result of an active splanchnic vasoconstriction [36]. Therefore, the increase of COP ratio by ultrafiltration, which means reduction of the central circulation, may be associated with the deterioration of the splanchnic oxygenation via a decrease in hepato-splanchnic blood flow. However, the mechanisms of the changes in cerebral and hepatic oxygenation during intradialytic blood transfusion with ultrafiltration during HD remain uncertain; therefore, further studies are needed to clarify the precise mechanisms underlying the results confirmed by the present study.

This study has several limitations. First, it was limited by the relatively small sample size. Second, we confirmed the changes in cerebral and hepatic oxygenation accompanied by the improvement in Hb levels during intradialytic blood transfusion; however, changes in tissue oxygenation from well-maintained Hb levels to a severe anemic status could not be observed. Finally, we could not directly measure the regional blood flow in the brain and liver during HD with intradialytic blood transfusion in this study. It would be better to evaluate the relationship between tissue oxygenation and regional blood flow in each organ during HD with transfusion, in addition to the evaluation of Hb increase and COP increase. Therefore, additional studies are needed to confirm the association between changes in tissue oxygenation and those in clinical parameters, including regional blood flow into systemic organs, induced by blood transfusion during HD.

In conclusion, throughout the intradialytic blood transfusion, tissue oxygenation in the brain and liver improved. Hepatic rSO_2 was significantly higher than cerebral rSO_2 at the end of HD. Furthermore, changes in cerebral oxygenation were associated with only the Hb increase induced by intradialytic blood transfusion, whereas those in hepatic oxygenation were associated with both the Hb increase induced by intradialytic blood transfusion (positive change) and the COP increase induced by ultrafiltration (negative change).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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