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Risk of Intradialytic Hypotension in Hemodialysis Patients with Different Residual Urine Volume

Qishu Li[1,2], **Xianfeng Wu**[1,2] **and Weiping Tu**[1,2*]

[1]*Department of Nephrology, The Second Affiliated Hospital of Nanchang University, Nanchang, China*

[2]*Department of Nephrology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China*

***Corresponding author:** Weiping Tu, Department of Nephrology, The Second Affiliated Hospital of Nanchang University, Nanchang, China, Tel: 0086-0791-86291976; E-mail: tuweiping6102@sina.com

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Abstract

Background: Relationship between intradialytic hypotension (IDH) and residual urine volume (RUV) in hemodialysis (HD) patients remained unclear. In the present study, we aimed to evaluate the risk of intradialytic hypotension in hemodialysis patients with different residual urine volume.

Method: This work was a prospective observational study of incident and prevalent HD patients. From January 1, 2013 to February 28, 2014, patients were recruited from a single HD center of the Second Affiliated Hospital of Nanchang University. Eligible patients were categorized into three groups: group A (RUV > 400 ml/24 hours), group B (RUV of 100-400 ml/24 hours) and group C (RUV < 100 ml/24 hours). A Logistic regression model was used to examine patient characteristics associated with predictive odds of RUV with 100-400 ml/24 hours and < 100 ml/24 hours. Hazard ratio (HR) of IDH was calculated by the Cox proportional hazards model for three groups.

Results: Totally, 150 HD patients were enrolled in this study, with mean follow-up of 9.9 ± 5.1 months. Older age, longer HD vintage and lower levels of hemoglobin were independently associated with RUV with 100-400 ml/24 hours, whereas thrice-weekly HD, longer HD vintage, diabetes and lower levels of phosphate were independently associated with RUV < 100 ml/24 hours in the study patients by multivariate Logistic regression analysis. During the follow-up period, 17.3% (26/150) patients developed IDH events, including 8.2% (5/61) in the group A, 15.9% (7/44) in the group B and 31.1% (14/45) in the group C. IDH incidence was significantly difference among three groups. Patients with RUV < 100 ml/24 hours had higher risk of IDH than those with RUV > 400 ml/24 hours, even when extensive demographics, comorbidities and lab adjustments were made. Similarly, in a maximally adjusted model, risk of IDH in patients with RUV of 100-400 ml/24 hours was 2.36 times than that in those with RUV > 400 ml/24 hours (95% CI 1.75-7.47, p=0.043).

Conclusion: HD patients with lower RUV may have an increased risk of presenting IDH, which suggested that preserving RUV may be conducive to preventing of IDH occurrence.

Keywords: Hemodialysis; Intradialytic hypotension; Outcomes; Residual renal function; Residual urine volume; Risk; Risk factor

Introduction

Hemodialysis (HD) patients, as a special population, have a distinct complication, i.e., intradialytic hypotension (IDH), which defined as both a fall blood pressure and the occurrence of symptoms requiring an intervention [1]. IDH is the most commonly reported adverse effect of outpatient HD [2,3], and is strongly associated with many adverse clinical events such as myocardial stunning, cerebral atrophy and increased mortality [4-6].Recently, it has been shown that mortality is increased in those HD patients prone to IDH [6].

Residual renal function (RRF) is a crucial predictor of survival in patients on dialysis treatments [7-9]. RRF, even at the lower levels of glomerular filtration rate in dialysis patients, plays a paramount role in clearance of uremic toxins, prevents volume overload and its sequelae, such as left ventricular hypertrophy and congestive heart failure [10-13]. Urine volume may serve as a simple indicator of RRF in HD patients. In fact, 24 hours RUV was only a part of RRF focusing on volume adjustment [14], which meant RRF was not exactly the same with 24 hours RUV. A previous study reported that RUV was independently associated with lower all-cause mortality and a trend towards lower CVD mortality in HD patients [9]. In those previous studies, however, IDH failed to be enrolled into CVD events. To our knowledge, there was a paucity of data regarding the risk of IDH in HD patients with different RUV. In the present study, we therefore aimed to assess the risk of IDH in incident and prevalent HD patients with different RUV.

Materials and Methods

Study design

This work was a prospective observational study of incident and prevalent HD patients. From January 1, 2013 to February 28, 2014, 172 incident and prevalent patients were recruited from a single HD center of the Second Affiliated Hospital of Nanchang University. Eligibility criteria included patients aged ≥ 18 years who had received HD for ≥3

months, except those who had conducted peritoneal dialysis previously, malignant disease or refused to give written consent. Thus, 150 patients were enrolled and analyzed in our study according to enrollment criteria. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Patients provided informed consent before study entry.

Data collection

Diuretics in eligible patients were discontinued for 7 days and information about RUV was available by questionnaires at the entry of study. Eligible patients were stratified into three groups according to RUV at baseline: group A (RUV > 400 ml/24 hours), group B (RUV with 100-400 ml/24 hours) and group C (RUV < 100 ml/24 hours).

The primary endpoint was IDH, which defined as both a fall blood pressure and the occurrence of symptoms requiring an intervention [1]. Baseline demographic and clinical data, including age, sex, HD frequency, HD vintage, diabetes, pre-existing CVD, hypertension as well as etiology of renal disease were recorded at the initiation of this study. Biochemical parameters in stable HD patients were measured per 3 months after HD therapy was initiated. Time-dependent parameters included dry weight, hemoglobin, serum uric acid, serum calcium, serum phosphate, intact parathormone, serum albumin, serum cholesterol and single pool Kt/v (spKt/v). Patients were followed up until death, transfer to peritoneal dialysis therapy, kidney transplantation, transfer of care from our center, or censoring on February 28, 2014.

To eliminate the influence on the data by confounding factors, patients maintained the HD sessions, which were conducted conforming to the NKF-DOQI clinical practice guidelines [15]. HD adequacy was evaluated by spKt/v, which was measured using the Daugirdas formula [16]. Patients who reported current use of oral hypoglycemic agents or insulin, and/or who had a clinical diagnosis of diabetes were considered to have diabetes [17]. Hypertension was recorded if the patient took antihypertensive drugs or had 2 separate blood pressure measurements ≥ 140/90 mmHg [18]. CVD was defined as any diagnosis of coronary artery disease, myocardial infarction, angioplasty, coronary artery bypass, congestive heart failure, cerebrovascular disease or peripheral arterial disease [17].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as percentages or frequencies. Comparison of means was performed using one way ANOVA test with Bonferroni adjustment. The Kruskal-Wallis test followed by Mann-Whitney U test was also used for non-parametric analysis. Comparison of qualitative variables was conducted by Pearson's $\chi 2$ test. Time to first IDH episode was recorded. A Logistic regression model was used to examine patient characteristics associated with predictive odds of RUV with 100-400 ml/24 hours and <100 ml/24 hours. Risk factors for IDH were investigated using Cox regression analysis with baseline characteristics and time-dependent covariates. Factors, which had a difference in relative risk of events by >10% (<0.90 or >1.1) in the univariate Cox regression analysis, were included in the multivariate Cox regression analysis. The rationale was to include factors that had a clinical significance and not simply statistical significance. Estimates of survival using the Kaplan-Meier estimator were used to describe the primary outcome. Additionally, Cox regression models were used to evaluate the risk of IDH in patients with different RUV (RUV > 400 ml/24 hours as a reference), initially without adjustment and subsequently adjusting for several groups of covariates. $P < 0.05$ was counted as statistically significant. Statistical analysis was performed using and SPSS 17.0 for Windows (SPSS Inc., Chicago, USA) and GraphPad Prism 5.0 software (GraphPad Software, Inc., California, USA).

Results

Patient characteristics at baseline

The demographic and clinical characteristics of HD patients were summarized in Table 1, and categorized according to RUV. A total of 150 HD patients were enrolled in this study (mean age, 61.2 ± 15.2 years), with mean follow-up of 9.9 ±5.1 months. Among these eligible patients, 61 (40.7%) were in the group A, 44 (29.3%) in the group B and 45 (30.0%) in the group C. Mean RUV was 521 ml/24 hours (range 0-2000 ml/24 hours) for all patients.

In the study period, one patient was transferred to peritoneal dialysis therapy, one patient received renal transplantation, and 9 transferred to other HD centers. Additionally, 6 deaths were recorded, including 4 CVD deaths (Figure 1).

	Group A (n=61)	Group B (n=44)	Group C (n=45)	p
Age (years)	58.7 ± 16.6	65.0 ± 14.4	60.9 ± 13.6	0.114
Male (%)	42(31.1)	33(25.0)	26(44.2)	0.211
Thrice-weekly HD (%)	5(8.2)	11(25.0)	26(57.8)	<0.001
HD vintage (months)	9.5(6.0-15.2)	9.0(2.5-16.2)	24.2(14.7-37.4)	<0.001
Dry weight	59.4 ± 9.4	57.1 ± 8.9	57.2 ± 12.7	0.424
Diabetes (%)	18(29.5)	13(29.5)	21(46.7)	0.13
Pre-existing CVD (%)	12(19.7)	16(36.4)	6(13.3)	0.027
Hypertension (%)	49(80.3)	36(81.8)	39(86.7)	0.685
Fluid removal(L/4 hours)	2.1 ± 0.7	3.0 ± 1.1	3.5 ± 1.0	0.041
Etiology of renal disease (%)				
Chronic glomerulonephritis (%)	25(41.0)	15(34.1)	14(31.1)	0.55
Diabetic nephropathy (%)	16(26.2)	12(27.3)	20(44.4)	0.101
Hypertensive nephrosclerosis (%)	12(19.7)	11(25.0)	3(6.7)	0.06
Other/unknown (%)	8(13.1)	6(13.6)	8(17.8)	0.778
Lab measurements				
Hemoglobin (g/L)	91.4 ± 15.9	81.7 ± 17.9	95.0 ± 19.7	0.001
BUN(mmol/L)	14.4 ± 3.7	19.8 ± 4.1	23.1 ± 4.2	0.048
Serum uric acid (μmol/L)	479.2 ± 111.8	479.3 ± 168.4	425.6 ± 76.1	0.053

Calcium (mmol/L)	2.0 ± 0.2	2.1 ± 0.3	2.1 ± 0.2	0.13
Phosphate (mmol/L)	1.7 ± 0.5	1.8 ± 0.6	2.0 ± 0.6	0.011
intact parathormone (pg/mL)	216.2(138.8-340.5)	154.2(122.4-309.5)	235.5(124.8-480.6)	0.289
Serum Albumin (g/L)	35.9 ± 4.1	35.4 ± 4.0	36.4 ± 4.9	0.523
Serum cholesterol (mmol/L)	3.9 ± 0.8	3.9 ± 1.1	4.1 ± 1.0	0.296
spKt/v	1.2 ± 0.3	1.2 ± 0.3	1.4 ± 0.4	0.006
Group A: RUV > 400 ml/24 hours; Group B: RUV with 100-400 ml/24 hours; Group C: RUV < 100 ml/24 ml. RUV: Residual Urine Volume; HD: Hemodialysis; CVD: Cardiovascular Disease; BUN: Urea nitrogen; spKt/v: Single Pool Kt/v.				

Table 1: Baseline characteristics by residual urine volume.

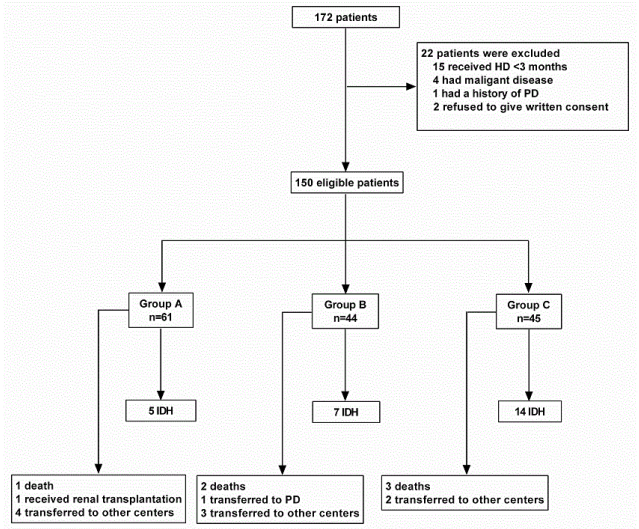

Figure 1: Study flow diagram. HD, hemodialysis; PD, peritoneal dialysis; IDH, intradialytic hypotension.

Risk factors for different RUV

Univariate Logistic regression analysis showed that age, HD vintage, pre-existing CVD and hemoglobin were associated with RUV with 100-400 ml/24 hours in the study population. After being adjusted for sex, diabetes, pre-existing CVD, spKt/v and calcium, older age, longer HD vintage and lower levels of hemoglobin were independently associated with RUV with 100-400 ml/24 hours in the study patients by multivariate Logistic regression analysis with a stepwise selection procedure (Table 2). Fluid removal, HD vintage, diabetes and age were associated with RUV > 400 ml/24 hours in the study population using univariate analysis. Diabetes and older age were independently associated with for RUV > 400 ml/24 hours in all patients after being adjusted for fluid removal and HD vintage. Thrice-weekly HD, HD vintage, diabetes, spKt/v, serum uric acid, calcium, phosphate, hemoglobin and intact parathormone were associated with RUV < 100 ml/24 hours in the study population using univariate analysis. Thrice-weekly HD (twice-weekly HD as a reference), longer HD vintage, diabetes and lower levels of phosphate were independently associated with for RUV < 100 ml/24 hours in all patients, when serum uric acid, calcium, hemoglobin, intact parathormone, and spKt/v adjustments were made.

	OR	95%CI	p
	RUV > 400 ml/24 hours		
Age (per 1 age increase)	1.05	1.02-1.09	0.001
Diabetes (yes/no)	2.01	1.32-3.01	0.011
	RUV with 100-400 ml/24 hours		
Age (per 1 age increase)	1.06	1.03-1.10	0.001
HD vintage (per 1 month increase)	1.03	1.01-1.07	0.002
Hemoglobin (per 1 g/L increase)	0.96	0.93-0.99	0.004
	RUV < 100 ml/24 hours		
Thrice-weekly HDb	7.18	2.66-19.38	<0.001
HD vintage (per 1 month increase)	1.08	1.04-1.12	<0.001
Diabetes (yes/no)	4.49	1.49-13.5	0.008
Phosphate (per 1 mmol/L increase)	2.37	1.13-6.11	0.042
aFactors, which had a difference in relative risk of events by >10% (<0.90 or >1.1) in the univariate analysis, were included in the multivariate analysis. bReference group is twice-weekly HD.			

Table 2: Adjusted OR of different residual urine volume in the study population[a].

IDH incidence and associated risk factors

In the whole process, 39 IDH episodes occurred in the study population, of which 9 (23.1%) were in the group A, 10 (25.6%) in the group B and 20 (51.3%) in the group C. Totally, 26 (17.3%) patients developed IDH events, including 5 (8.2%) in the group A, 7 (15.9%) in the group B and 14 (31.1%) in the group C. IDH incidence was significantly difference among three groups (p=0.008). Additionally, IDH incidence increased with age in the study population (p=0.024), and was similar between the incident and prevalent HD patients (17.1% vs. 17.5%, p=0.954).

	HR	95%CI	p
	RUV > 400 ml/24 hours (n=61)		
Thrice-weekly HDb	2.12	1.09-6.39	0.021
Diabetes (yes/no)	1.36	1.16-6.27	0.043
Pre-existing CVD (yes/no)	1.42	1.12-7.81	0.015
	RUV with 100-400 ml/24 hours (n=44)		
Thrice-weekly HDb	2.25	1.10-5.64	0.019
HD vintage (per 1 month increase)	1.02	1.01-1.08	0.037
Diabetes (yes/no)	1.43	1.09-6.83	0.039

	RUV < 100 ml/24 hours (n=45)		
Age (per 1 age increase)	1.03	1.01-1.09	0.025
Thrice-weekly HDb	2.24	1.13-5.16	0.017
Diabetes (yes/no)	1.63	1.24-5.97	0.036
Fluid removal(per 1 L increase)	1.92	1.24-2.52	0.012
Uric acid (per 100 μmol/L increase)	1.07	1.02-2.09	0.028

aFactors, which had a difference in relative risk of events by >10% (<0.90 or >1.1) in the univariate analysis, were included in the multivariate analysis. bReference group is twice-weekly HD.

Table 3: Adjusted HR of IDH in HD patients with different residual urine volume[a].

Although there was no statistically difference in IDH incidence between diabetic HD patients and those non-diabetes (p=0.176), the diabetes had remarkably higher IDH incidence than their counterparts (23.1% vs. 14.3%).

Univariate Cox regression analysis showed that older age, thrice-weekly HD (twice-weekly HD as a reference), diabetes, pre-existing CVD and serum phosphate were associated with IDH in patients with RUV > 400 ml/24 hours. After being adjusted for age and serum phosphate, thrice-weekly HD (twice-weekly HD as a reference), diabetes and pre-existing CVD were independently risk factors for IDH in these patients by multivariate analysis (Table 3). Thrice-weekly HD (twice-weekly HD as a reference), HD vintage and diabetes were independently predictors for IDH in those in the group B, when age, serum albumin and intact parathormone adjustments were made. In addition, older age, thrice-weekly HD (twice-weekly HD as a reference), diabetes, greater fluid removal and higher levels of serum uric acid were independently associated with increased risk of IDH in patients in the group C, after being adjusted for HD vintage, pre-existing CVD and serum albumin.

Risk of IDH in HD patients with different RUV

Associations of RUV with IDH with defined models (with the group A as the reference group) are listed in Table 4.

	RUV with 100-400 ml/24 hours (n=44)			**RUV < 100 ml/24 hours (n=45)**		
	HR	95%CI	p	HR	95%CI	p
Unjusted	2.3	1.73-7.26	0.045	3.38	1.21-9.40	0.02
Model 1	2.31	1.73-7.28	0.043	3.37	1.21-9.39	0.02
Model 2	2.15	1.68-6.78	0.049	3.35	1.20-9.32	0.021
Model 3	2.36	1.75-7.47	0.043	4.55	1.59-13.0	0.005

Note: reference group was RUV > 400 mL/24 h (n=61). Model 1: adjusted for age, sex, thrice-weekly HD, HD vintage and dry weight. Model 2: adjusted for model 1 covariates and diabetes, pre-existing CVD and hypertension. Model 3: adjusted for model 2 covariates and hemoglobin, serum uric acid, calcium, phosphate, intact parathormone, albumin, cholesterol and spKt/v.

Table 4: Relationship between residual urine volume and IDH.

Regardless of the adjustment method used, patients in the group C were significantly associated with higher IDH compared to those in the group A (HR 3.38, 95%CI 1.21-9.40, p=0.020). Patients in the group B were also significantly associated with higher IDH compared with those in the group A (HR 2.30, 95%CI 1.73-7.26, p=0.045). In model 3, which was a maximally adjusted model including age, sex, HD vintage, dry weight, diabetes, pre-existing CVD, hypertension, hemoglobin, serum uric acid, calcium, phosphate, intact parathormone, albumin, cholesterol and spKt/v, adjusted HR for IDH was 4.55 (95% CI 1.59-13.00, p=0.005), when RUV decreased from more than 400 ml/24 hours to less than 100 ml/24 hours. Similarly, in a maximally adjusted model 3, risk of IDH in patients in the group B was 2.36 times than that in the group A (95% CI 1.75-7.47, p=0.043).

Figure 2 showed Kaplan-Meier survival curves of HD patients with different RUV. In crude analysis, a significant difference between different RUV and their association with IDH was found, with the lowest survival in patients with RUV less than 100 ml/24 hours (group C: Log rank=6.02, p=0.039).

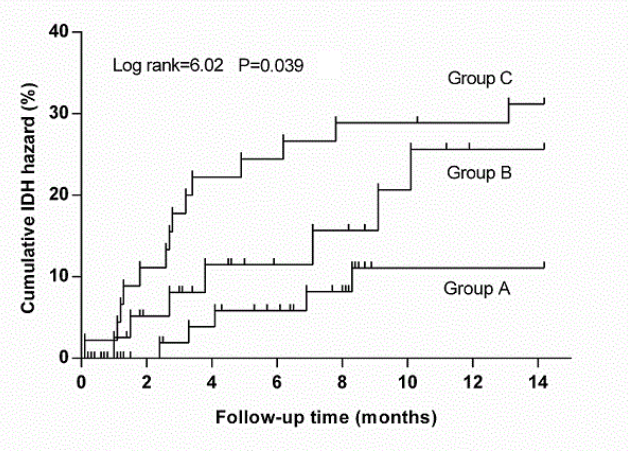

Figure 2: Kaplan Meier estimates of IDH among HD patients with different RUV. Group A: RUV > 400 ml/24 hours; Group B: RUV with 100-400 ml/24 hours; Group C: RUV < 100 ml/24 ml. HD: Hemodialysis; RUV: Residual Urine Volume; IDH: Intradialytic Hypotension.

Discussion

The results showed that patients with RUV < 100 ml/24 hours had 4.55-fold higher risk of IDH than those with RUV > 400 ml/24 hours. Those with RUV with 100-400 ml/24 hours had also 2.36 times higher risk of IDH than those with RUV > 400 ml/24 hours.

In the last decades, many studies have approached to the conclusion that preservation of RRF is important in the pre-dialysis period, as well as after initiating dialysis [19]. Longer preservation of RRF provided a better small and middle molecule removal, prevented volume overload and its sequelae, improved arterial pressure control, diminished risk of vascular and valvular calcification due to better phosphate removal [20,21]. Deterioration of RRF contributes to worsening of inflammation, anemia and malnutrition [22,23]. Urine volume may serve as a simple indicator of RRF in HD patients. A single-center US study of 114 prevalent HD patients confirmed the association of any

urine output (>100 ml per day) with a 65% lower mortality over the subsequent 2 year period [24]. Recently, a national cohort study of the US hemodialysis population reported that baseline urine volume was not associated with survival, whereas urine volume at year 1, indicating preserved RRF, was independently associated with lower all-cause mortality (HR=0.70) and a trend towards lower CVD mortality (HR=0.69) in HD patients [9]. In the present study, we found that older age, longer HD vintage and lower levels of hemoglobin were independently associated with increased risk of RUV with 100-400 ml/24 hours, whereas thrice-weekly HD (twice-weekly HD as a reference), longer HD vintage, diabetes and higher serum phosphate conferred an increased risk of RUV < 100 ml/24 hours in HD patients. These results suggested that clinical nephrologists may take proper medical methods for prevention of progression of RUV by modulating these modifiable risk factors, such as hemoglobin, HD frequency and serum phosphate.

IDH is an important side effect of HD and continues to be a leading problem, and it has a negative impact on health-related quality of life [1,6,25]. It is generally known that the major causes of hemodialysis-associated hypotension involve old age, poor cardiac reserve, atherosclerosis, removal of vast volume of fluid and an impaired sympathetic response. Koch et al. [26] showed that the risk of cardiac death was increased when two or three hypotensive episodes occurred per week [26,27]. Even in a study of patients using antihypotensive medications, hemodialysis hypotension was a significant predictor for death rate in multivariate analysis [6]. Previous studies found that IDH was strongly correlated with many adverse clinical events such as myocardial stunning, cerebral atrophy and increased mortality [4-6]. Shoji et al. [6] reported that mortality is increased in those HD patients prone to IDH [6]. Nonetheless, risk of IDH in HD patients with different RUV remained unknown. In this study, we found that patients with RUV < 100 ml/24 hours had higher risk of IDH than those with RUV > 400 ml/24 hours. Similarly, those with RUV of 100-400 ml/24 hours had also higher risk of IDH as compared with those with RUV > 400 ml/24 hours. Our results suggested that patients with lower RUV may have higher chances of presenting IDH. However, IDH was not uniformly defined, regularly aggregated, or reported in US outpatient dialysis facilities. The lack of routine reporting hindered the medical management of IDH and made attending nephrologists not notice the frequency their patients undergo IDH. These discrepancies in reporting offer an enticing potential approach to improve patient's clinical conditions. Of note, in the present study, IDH was defined according to the European Best Practice Guidelines [1]. Although this definition appears relatively straight forward, few previous studies have used this rigorous definition during research studies. Disparities of IDH defined also appear to be a major source of variation from one study to the next. Thus, variable definitions also generate problems with interpretation of the study findings.

From a study with a mean follow up of 18 months, compared with patients having lower RRF on thrice-weekly HD, patients with higher RRF on twice-weekly HD were had a slower decline of residual glomerular filtration rate [28]. Given the adverse effect of ischaemia on RRF, one plausible explanation is that this is associated with the lower incidence of intradialytic hypotensive episodes in this study. More specifically, in a recent study, we found that patients on thrice-weekly HD may be associated with increased risk of IDH as compared to those with twice-weekly HD [29]. In that study, patients with thrice-weekly HD had 2.47 fold risk of IDH than those with twice-weekly HD, even after being adjusted for extensive demographics, comorbidities and lab adjustments. In the present study, thrice-weekly HD (twice-weekly HD as a reference) remained independently associated with increased risk of IDH in patients with different RUV. Among patients with RUV > 400 ml/24 hours, patients with thrice-weekly HD had 2.12 times risks of IDH as compared to those with twice-weekly HD, and similar results were found among those with RUV of 100-400 ml/24 hours (HR=2.25) and RUV < 100 ml/24 hours (HR=2.31). In additional, a multicenter prospective, observational cohort study found that the fall in intradialysis blood pressure in diabetic patients was significantly greater than in nondiabetic patients [6] reported that older age, female gender and diabetes were independently associated with increased IDH frequency in HD patients [30]. In our study, thrice-weekly HD (twice-weekly HD as a reference) and diabetes were independently predictors for IDH in HD patients, irrespective of different RUV. Longer HD vintage conferred a higher independently risk of IDH in those with RUV with 100-400 ml/24 hours, whereas older age and higher levels of serum uric acid conferred an increased risk of IDH in those with RUV < 100 ml/24 hours, which suggested that fewer HD frequency and lower serum uric acid may be beneficial to prevention of IDH.

There were also some limitations in our study. Firstly, this was a prospective single-center study with a small number of participants and limited follow-up. Further prospective, multi-center, larger, longitudinal study with longer follow-up is required to further delineate the relationship between IDH and RUV. In addition, we failed to analyze weekly Kt/v in this study. K-DOQI guidelines recommend 2 to 6 HD sessions per week, provided that the HD schedule is tailored to achieve a minimum standard Kt/V of 2.0 per week [15]. In our study, mean value of 1.26 of spKt/v was greater than 1.2 in HD patients (data not shown), which suggested that adequacy of dialysis was acceptable in HD patients.

This study revealed that HD patients with lower RUV may be associated with an increased risk of IDH. The association remained robust even after being adjusted for baseline characteristics, comorbidities and lab measurements, which suggested that HD patients should pay attention to preserving RUV for prevention of IDH. Although the use of RUV may be insufficiently precise to be used as a predictor for RRF, it may be more convenient for nephrologists to assess the risk of IDH in HD patients in clinical practice.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgments

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