Effect of Dialysate Glucose Concentration on Hepcidin Clearance in Maintenance Hemodialysis Patients

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Keywords. hepcidin, catecholamine, glucose-free dialysate, glucose-containing dialysate

Introduction. Hepcidin is a key regulator of iron homeostasis, takes part in pathophysiology of anemia and cardiovascular disease in maintenance hemodialysis (MHD) patients. The aim of this study was to compare the effect of glucose-free and glucose-containing dialysate on the clearance of hepcidin-25 during a hemodialysis (HD) session and discuss its potential mechanism in MHD patients.
Materials and Methods. In a longitudinal interventional study of 30 stable MHD patients without diabetes, we measured serum hepcidin-25 and plasma catecholamines (adrenaline, noradrenaline, and dopamine) during HD session using glucose-free dialysate and then switched to 5.55 mmol/L glucose-containing dialysate. One-way analysis of variance (ANOVA) was used to identify the effect of two dialysates on the intra-dialysis changes of hepcidin-25 and catecholamines. Spearman and Pearson correlation coefficients were performed to detect the relationships between hepcidin-25 and catecholamines.
Results. Glucose-free dialysate achieved a greater reduction of hepcidin-25 than 5.55 mmol/L glucose-containing dialysate in a single bicarbonate HD session [−8.43 (-15.44 to -1.42) vs. 0.46 (−6.09 to 7.00)%, $P < .05$]. The intra-dialysis changes of catecholamines showed no significant differences between the two dialysates. The serum hepcidin-25 levels were positively associated with plasma catecholamines levels at pre-, intra- and post-HD (R = 0.22~0.62 with $P < .05$).
Conclusions. Our findings suggest that glucose-containing dialysate might up-regulate hepcidin-25 synthesis through activation of the sympathetic nervous system or oxidative stress, possibly mediated by increased production of catecholamines. Adequately designed studies are needed to confirm and reveal the mechanisms of dialysate glucose concentration on hepcidin-25 kinetics during HD sessions.

IJKD 2019;13:113-9
www.ijkd.org

Original Paper

INTRODUCTION

Iron deficiency anemia (IDA) is an important and frequent problem in patients undergoing maintenance hemodialysis (MHD). In MHD patients, increased blood loss and compromised gastrointestinal iron absorption result in absolute iron deficiency, meanwhile, reticuloendothelial cell iron blockade causes the defect to deliver iron to marrow for erythropoiesis, that is defined as functional iron deficiency.[1] Intravenous iron therapy is frequently prescribed for IDA in MHD patients, while it could bring a state of positive iron balance, aggravate functional iron deficiency, and lead to an overt risk of clinically relevant iron toxicity.[2]

Hepcidin, encoded by the HAMP gene, a protein produced in liver, is a negative regulator of iron utilization, through inhibiting intestinal iron absorption and iron release from macrophages and hepatocytes.[3] The circulating hepcidin could be regulated by iron stores, inflammation, erythropoiesis, hypoxia as well as decreased renal clearance.[2] Previous studies reported that increased serum levels of hepcidin could reduce iron availability for erythropoiesis in MHD patients, suggested that anti-hepcidin strategies could improve anemia management.[4,5] Hepcidin-25 is the active form of hepcidin, and plays an important role in functional iron deficiency.[6] Several studies on the clearance of hepcidin-25 during a hemodialysis (HD) session reported that its clearance ratio could be influenced by various factors, such as membranes of dialyzers, dialysis modality, single-pool Kt/V (spKt/V) and erythropoietin dose.[7-11] However, the effect of dialysate composition on the kinetics of hepcidin-25 removal through an HD session remains unknown.

Glucose-containing dialysate has been used widely to avoid HD-induced hypoglycemia.[12] In China, most of HD centers still use glucose-free dialysate nowadays, in part due to the considerations of infection control and medical expenses. Chinese researchers also reported that glucose-containing dialysate was beneficial to maintain blood glucose and blood pressure (BP) during HD sessions, no matter whether these patients had diabetes or not.[13,14] The purpose of this study was to compare the effect of glucose-free and glucose-containing dialysate on the clearance of hepcidin-25 during an HD session, and discuss its potential mechanism in MHD patients.

MATERIALS AND METHODS

Participants

This was a longitudinal interventional study in clinically stable MHD patients without diabetes from hemodialysis (HD) center of the Xuzhou Central Hospital (Xuzhou, China). Inclusion criteria were: 1) patients with ESRD; 2) aged 18-80 years; 3) received HD for more than 3 months. Exclusion criteria were: 1) malignant disease, or overt infection/inflammation; 2) hospital admission within the preceding 3 months for any cause; 3) refusal to sign written consent. All patients were on standard HD with treatment duration/session of 4 hours, using low-flux polyethersulfone dialyzer and final glucose-free dialysate (bicarbonate 35 mmol/L, K^+ 2.0mmol/L, Ca^{2+} 1.5 mmol/L, Mg^{2+} 0.5 mmol/L, without glucose) for 2 weeks (six sessions). After that, the patients were switched to a 5.55 mmol/L glucose-containing dialysate (rest components of dialysate remained unchanged) for 2 weeks (six sessions). The dialyses within the frame of the study were performed at the same time and same weekday each time (morning dialyses). This study was performed from June to December 2017. The protocol was approved by the ethical committee of the Xuzhou Central Hospital, Medical College of Southeast University (Approval No. ZXXY-LJ-20150115-001).

Data Collection and Measurements

Demographic and clinical data were recorded. Intradialytic hypertension, hypotension, and hypoglycemia were defined as previously discussed.[15-17] The spKt/V was determined by two-point urea modeling based on the intradialytic reduction in blood urea and intradialytic weight loss. Blood samples were taken at pre-dialysis, 120 minutes after HD session started and the end of HD session, from the arterial end of dialysis pathway after turning off ultrafiltration for 2 minutes. Serum hepcidin-25 was measured using competitive enzyme-linked immunosorbent assay kits[18] (Cat. CSB -E14239h, Cusabio, China), with a coefficient of variation (CV) < 10% in both inter- and intra-assay precision analyses. Plasma catecholamines were measured using a protocol based on high-performance liquid chromatography (HPLC), including adrenaline, noradrenaline, and dopamine.[19] The effect of hemodialysis session was expressed as the percentage (%) differences between serum/plasma concentrations at pre-dialysis (Cpre) and 120 minutes after dialysis started (C120) or at the end of dialysis session (Cpost). The dialytic clearance of hepcidin-25 was calculated as follows: (C120 or Cpost – Cpre) / Cpre × 100%, a negative value indicating a drop of serum concentration during dialysis. C120 and Cpost values were adjusted by the ratio of total serum protein concentration at Cpre, C120, and Cpost.[11]

Statistical Analysis

Patients' baseline demographics, clinical

characteristics, and laboratory measurements were summarized as proportions, medians [interquartile range (IQR)] or mean (± SD), and analyzed using the t-test or Wilcoxon's test for paired data with Bonferroni's correction. One-way analysis of variance (ANOVA) was used to identify the effects of two dialysates on the intra-dialysis percentage of changes of hepcidin-25 and catecholamines. Spearman and Pearson correlation coefficients were performed to detect the relationships between the serum levels of hepcidin-25 and plasma levels of catecholamines. A two-sided *P* value < .05 was defined as statistically significant. All statistical analyses were performed using SAS system, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 30 MHD patients without diabetes were enrolled in the study, the median age was 45 years (range 40.5 to 50.5), and 56.7% of the subjects were female (13 males / 17 females), the median vintage of HD was 55.5 months (range 47 to 74.5 months). Blood pressure at 120 minutes after starting dialysis was significantly higher in HD sessions with 5.55 mmol/L glucose-containing dialysate than with glucose-free dialysate, while no intradialytic hypertension or hypotension, or hypoglycemia event was observed during this study. Plasma levels of dopamine at intra- and post-HD were higher in HD sessions with 5.55 mmol/L glucose-containing dialysate than with glucose-free dialysate. There were no differences in spKt/V, blood glucose, hepcidin-25, adrenaline, and noradrenaline between glucose-containing and free dialysates groups (Table 1).

Figure 1A showed the intra-dialysis percentage of change in serum hepcidin-25 levels, the glucose-free dialysate achieved a greater reduction of hepcidin-25 than 5.55 mmol/L glucose-containing dialysate in a single bicarbonate HD session [−8.43 (-15.44 to -1.42) vs. 0.46 (−6.09 to 7.00)%, *P* < .05]. The intra-dialysis percentage of change of dopamine and adrenaline showed similar trends as hepcidin-25. However, by the end of HD sessions, the plasma levels of all catecholamines (adrenaline, noradrenaline, and dopamine) showed no significant differences between glucose-free and glucose-containing dialysates (Figure 1B, C, and D).

Furthermore, the positive correlations between serum hepcidin-25 and plasma catecholamines were found. Pearson correlation showed that hepcidin-25 levels were not only positively associated with dopamine levels at pre-, intra-, and post-HD (R = 0.38, 0.22 and 0.62, respectively, *P* < .05), but also positively associated with noradrenaline levels at pre-, intra-, and post-HD (R = 0.38, 0.34 and 0.32, respectively, *P* < .05). Similar results were observed in the analyses by the Spearman correlation coefficient (Table 2).

DISCUSSION

Hepcidin-25 regulates iron metabolism through inhibiting intestinal iron absorption and iron release from reticuloendothelial cells causes more severe anemia in patients with chronic kidney disease (CKD) and takes part in the pathophysiology of atherosclerosis and cardiovascular events in MHD patients.[20-23] Thus, reducing hepcidin-25 burden could be a therapeutic target for anemia in patients with CKD or MHD. Hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI) has emerged as novel oral therapies for anemia in CKD patients.

Table 1. Hepcidin-25 and Catecholamines Pre-dialysis, 120 min After Starting Dialysis and After Dialysis [means ± SD]

	Glucose-free Dialysate			5.55 mmol/L Glucose-containing Dialysate		
	Pre-dialysis	120 min after Starting Dialysis	Post-dialysis	Pre-dialysis	120 min After Starting Dialysis	Post-dialysis
spKt/V			1.48 ± 0.24			1.48 ± 0.22
SBP (mmHg)	126.3 ± 5.41	123.73 ± 4.89	132.77 ± 10.51	127.43 ± 6.25	128.3 ± 10.86[a]	137.13 ± 7.20
DBP (mmHg)	77.83 ± 4.46	75.33 ± 5.59	82.77 ± 9.3	79.83 ± 5.17	80.07 ± 6.02[a]	86.03 ± 6.99
Blood Glucose (mmol/L)	6.3 ± 0.94	7.5 ± 0.31	6.65 ± 0.86	5.97 ± 1.01	7.10 ± 0.62	6.81 ± 0.74
Hepcidin-25 (ng/mL)	54.06 ± 17.47	41.34 ± 11.02	47.25 ± 10.38	44.99 ± 13.37	38.85 ± 14.14	45.14 ± 15.21
Dopamine (ng/L)	72.49 ± 16.54	40.47 ± 6.26	37.65 ± 8.93	64.53 ± 21.98	43.77 ± 5.39[a]	43.46 ± 11.69[b]
Adrenaline (ng/L)	49.11 ± 8.38	44.06 ± 4.82	53.87 ± 9.72	50.77 ± 11.97	45.97 ± 11.15	54.45 ± 6.57
Noradrenaline (ng/L)	1946.26 ± 316.72	1795.56 ± 610.43	1353.04 ± 368.99	1868.99 ± 342.7	1808.22 ± 555.81	1346.53 ± 345.73

[a]Pre-dialysis versus 120 min after starting dialysis (*P* < .05)
[b]Pre-dialysis versus post-dialysis (*P* < .05)
Abbreviation: spKt/V, single-pool Kt/V; SBP, systolic blood pressure; DBP, diastolic blood pressure

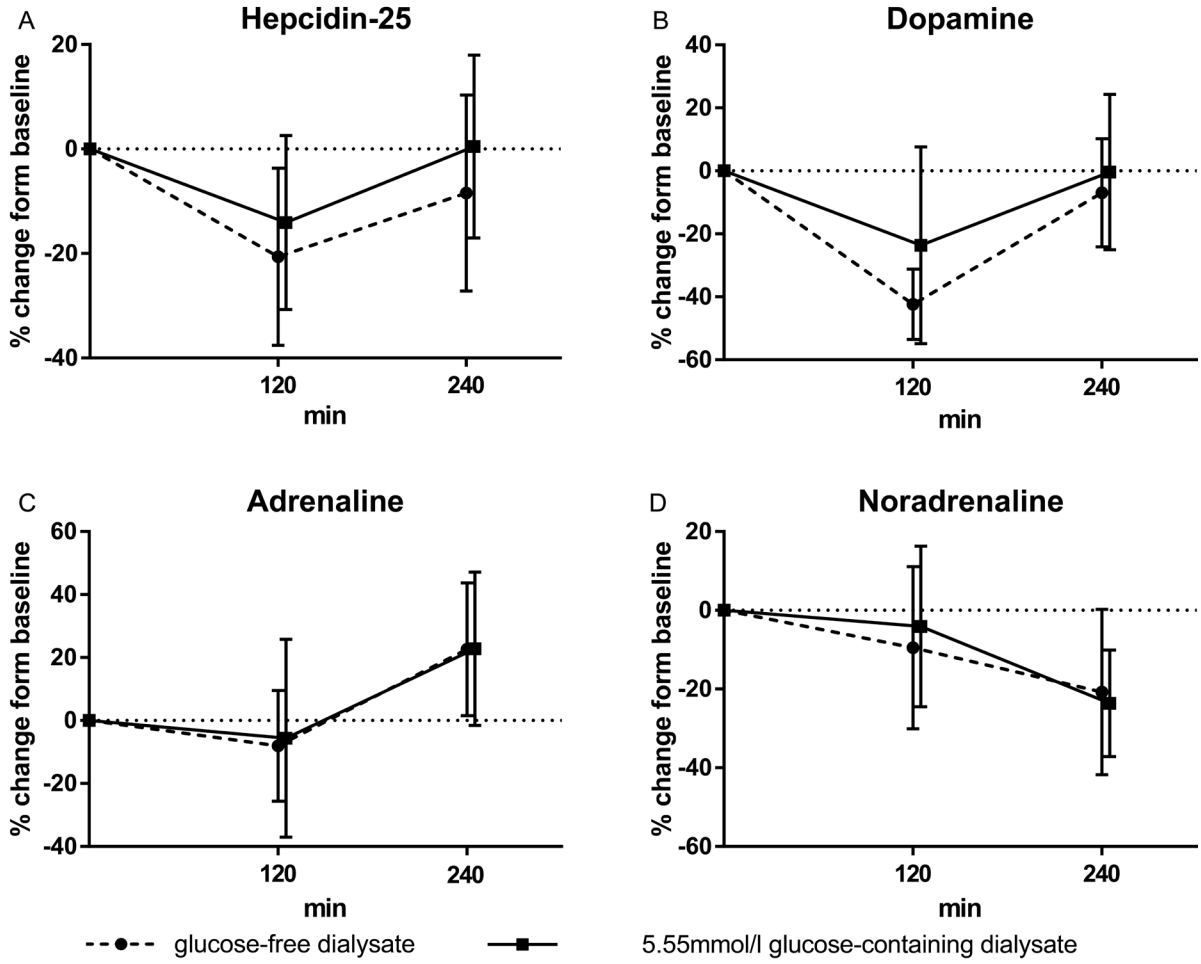

Figure 1. Percent changes in levels of hepcidin-25 and catecholamines during a single hemodialysis session with glucose-free dialysate (circle point, dotted line) and 5.55 mmol/L glucose-containing dialysate (square point, continuous line). The post-dialysis percentage change in hepcidin-25 levels obtained with glucose-free dialysate differed significantly from that of 5.55 mmol/L glucose-containing dialysate ($P < .05$). While no differences emerged between the two dialysates in terms of the intra-dialysis percentage changes for dopamine, adrenaline, and noradrenaline.

Table 2. Correlations Between Hepcidin-25 and Catecholamines

	Pre-DA	Intra-DA	Post-DA	Pre-A	Intra-A	Post-A	Pre-NA	Intra-NA	Post-NA	Pre-HEP	Intra-HEP	Post-HEP
Pre-DA		0.5**	0.53**	0.42**	0.44**	0.55**	0.53**	0.49**	0.47**	0.35*	0.18	0.18
Intra[a]-DA	0.41**		0.63**	0.46**	0.49**	0.55**	0.38*	0.51**	0.47**	0.22	0.24	0.17
Post-DA	0.39**	0.54**		0.43**	0.34*	0.51**	0.28*	0.34*	0.41*	0.52**	0.49**	0.51**
Pre-A	0.33**	0.23**	0.29**		0.3*	0.74**	0.57**	0.41*	0.44**	0.33*	0.34*	0.37*
Intra-A	0.3**	0.26**	0.13**	0.44*		0.5**	0.34*	0.42**	0.35*	0.17	0.16	0.13
Post-A	0.54**	0.49*	0.4*	0.65**	0.37**		0.5**	0.46**	0.36*	0.35*	0.35*	0.28*
Pre-NA	0.52**	0.25**	0.22**	0.5**	0.29**	0.47**		0.74**	0.82**	0.33*	0.21	0.33*
Intra-NA	0.48*	0.42*	0.28**	0.28*	0.33**	0.42**	0.78**		0.77**	0.39*	0.32*	0.29*
Post-NA	0.42**	0.32*	0.24*	0.22**	0.18**	0.27**	0.83**	0.8**		0.36*	0.20	0.34*
Pre-HEP	0.38**	0.21*	0.49**	0.26*	0.16*	0.33**	0.38**	0.4**	0.35*		0.79**	0.82**
Intra-HEP	0.08	0.22**	0.55*	0.02	0.22*	0.32*	0.24*	0.34*	0.21**	0.79**		0.84**
Post-HEP	0.06	0.17**	0.62*	0.01	0.15*	0.03	0.34*	0.01	0.32**	0.81**	0.88**	

Spearman Correlations in the Top Diagonal and Pearson Correlations in the Bottom Diagonal;
[a] Intra- represented 120 min After Starting Dialysis;
Abbreviations: DA, dopamine; NA, noradrenaline; A, adrenaline; HEP, hepcidin-25;
*$P < .05$
**$P < .01$

These agents could not only stimulate endogenous EPO synthesis, but also regulate iron metabolism by reducing serum hepcidin-25 in a dose-dependent manner to increase iron availability.[24-26] The clearance of hepcidin-25 during dialysis procedure could be another way to reduce hepcidin-25 burden in MHD patients.

Hepcidin-25 is a middle-molecular-weight substance with a molecular weight of 2,791 Da and the removal by dialysis has been demonstrated with varying degrees of efficiency. The clearance is mild in low-flux HD, intermediate by high-flux HD, and elevated in OL-HDF.[9] Ashby et al, reported that hepcidin-25 reduction was strongly related with spKt/V,[10] and Tessitore et al, showed that hepcidin-25 synthesis can be up-regulated by inflammatory status due to the effect of dialyzer membrane.[11] In our study, the intra-dialysis percentage of change in hepcidin-25 levels were used to reflect the clearance of hepcidin-25 in a single bicarbonate HD session. Our results indicated that the clearance of hepcidin-25 could be influenced by dialysate glucose concentration. During HD sessions with similar levels of spKt/V, glucose-free dialysate achieved better clearance of hepcidin-25 than glucose-containing dialysate.

The benefits of glucose-containing dialysate have been widely studied and reported. The glucose-containing dialysate could prevent acute hypoglycemia, hyperglycemia, and fluctuations of BP on HD days, particularly in patients with diabetes.[12] High concentration of glucose in dialysate (e.g., 11.0 mmol/L glucose) could bring hyperglycemia, lead to unfavorable metabolic effects, such as activation of parasympathetic system, overt oxidative stress, and up-regulation of inflammatory cytokines.[27-29] Thus, we selected 5.55 mmol/L glucose-containing dialysate in our study. Previous studies demonstrated that glucose-containing dialysate was beneficial to maintain blood glucose and BP during HD sessions.[12-14,27-29] However, our study showed no difference in blood glucose levels between the two dialysates, while BP levels were higher at intra-HD with glucose-containing dialysate than with glucose-free dialysate. There was no event of intradialytic hypertension, hypotension or hypoglycemia during all HD sessions.

To discuss the mechanisms of different clearance ratios of hepcidin-25, we measured the plasma catecholamines, which reflect the activation of sympathetic nervous system (SNS), and have been reported to be influenced by dialysate glucose concentration.[12] The auto-oxidation of catecholamines could mediate and induce oxidative stress, which is also a potential risk stimulated by glucose-containing dialysate.[27,30] In our study, plasma dopamine levels at intra- and post- HD were higher in HD sessions with 5.55 mmol/l glucose-containing dialysate than in HD sessions with glucose-free dialysate, and positive correlations existed between hepcidin-25 and catecholamines at pre-, intra- and post-HD. Furthermore, the hepcidin-25 levels decreased at 120 minutes, increased again by the end of HD session, the similar trends were also seen in the intra-dialysis percentage of change of dopamine and adrenaline. These results suggested that circulating hepcidin-25 level was decreased at the beginning of dialysis, then the synthesis of hepcidin-25 exceeded its clearance. The synthesis of hepcidin-25 might be upregulated by the activation of SNS or oxidative stress, particularly in the middle and late period of an HD session. The activation of SNS or oxidative stress might be mediated by increased production of catecholamines, in part due to the change of glucose concentration in the dialysate.

There are limitations in our study. The patients in our study had relatively low risks for acute events of intradialytic hypertension, hypotension, and hypoglycemia because they were young, in stable clinical condition and without diabetes. However, these findings suggested that glucose-containing dialysate might not be an optimal option for all MHD patients when its related low clearance ratio of hepcidin-25 was taken into consideration. The individualized dialysate is needed to achieve better clinical outcomes.

In conclusion, the clearance of hepcidin-25 could be influenced by dialysate glucose concentration, glucose-free dialysate may achieve a better clearance ratio than glucose-containing dialysate during a single HD session. The hepcidin-25 might be up-regulated by the activation of SNS or oxidative stress, which was possibly mediated by increasing catecholamines, in part due to the change of glucose concentration in dialysate. Further studies in larger cohorts of MHD patients with diabetes and non-diabetes should be performed to confirm these findings and reveal the mechanisms of dialysate

glucose concentration on hepcidin-25 kinetics during HD sessions.

FUNDING

This study was supported by grants to Ling Sun from the National Natural Science Foundation of China (81600540) and Natural Science Foundation of Jiangsu Province (BK20150224), Science and Technology Foundation of Xuzhou City (KC16SL119), Jiangsu Entrepreneurial Innovation Program, Jiangsu Six Talent Peaks Project, Jiangsu Health International (regional) exchange support program, and Xuzhou Entrepreneurial Innovation Program.

CONFLICTS OF INTEREST

None declared.

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Received July 2018
Revised September 2018
Accepted October 2018