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Cerebral hemodynamics among non-diabetic hemodialysis patients

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Abstract

Background: Cerebrovascular accidents and cognitive impairment is a frequent complication of end-stage renal disease (ESRD) on regular hemodialysis (HD).

Objective: To evaluate cerebral circulation hemodynamics in non-diabetic prevalent hemodialysis patients by transcranial Doppler (TCD).

Patients and methods: The cross-sectional study included 50 ESRD patients on regular hemodialysis > 6 months in Ain Shams University Hospitals, Cairo, Egypt. Diabetic patients; chronic liver disease patients Child-Pugh class B or C; smokers; history of evident of cardiac, peripheral, or cerebrovascular insult; uncontrolled hypertension; anemia; collagen disease; and active infection were excluded from the study. An assessment of cerebral circulation hemodynamics by TCD in non-dialysis day to examine mean flow velocity (MFV) in the middle cerebral artery (MCA) and posterior cerebral artery (PCA).

Results: An assessment of cerebral circulation hemodynamics revealed that 16 (32%) of the patients showed decrease MFV in MCA and 30 (60%) were normal. Regarding MFVs in PCA, 13 (26%) of the patients showed decrease MFVs, 33 (66%) were normal, and 4 (8%) of the patients failed due to poor bone window, significant reduction of MCV and PCA velocities in HD with urea reduction ratio < 65%, and a significantly negative correlation of MFV, PCA, and hemoglobin level ($P < 0.05$).

Conclusion: There is a high frequency rate of decreased MCA and PCA MFV (32%, 28%), respectively, among non-diabetic prevalent hemodialysis patients with significant correlation to hemodialysis adequacy.

Keywords: Cerebral circulation, Hemodynamics, Hemodialysis

Introduction

Patients with end-stage renal disease (ESRD) are at increased risk of cerebrovascular diseases such as encephalopathy, cerebrovascular strokes, cognitive impairment, and dementia with a risk higher than the general population [1]. The risk of stroke as a frequent complication of uremia, which can result from acute cerebral blood flow reduction, is five times higher in dialysis patients than the general population [2].

The global cerebral perfusion rate was reported to be declined from a baseline of 34.5 mL/100 g/min to 30.5 mL/100 g/min at the end of dialysis by PET-CT. A lower cerebral blood flow is associated with hemodialysis treatment-related factors, a higher ultrafiltration volume, a higher tympanic temperature, and a lower partial pressure of carbon dioxide [3].

Transcranial Doppler ultrasound is a non-invasive technique for the evaluation of cerebral blood flow velocities with the advantages of the possibility of continuous, real-time recording. Many studies reported the significant correlation between relative changes in cerebral blood velocity and changes in cerebral blood flow over a wide range of flow velocities, and therefore, it seems that transcranial Doppler recording of blood velocity can provide a useful indication of the real changes in the underlying cerebral blood flow [4].

There were limited studies about the assessment of cerebral blood flow among HD patients in non-dialysis day.

The aim of this study is to evaluate cerebral hemodynamics in prevalent non-diabetic hemodialysis patients by transcranial Doppler (TCD).

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Patients and methods

Study population

The study subjects included 50 end-stage renal disease (ESRD) patients on hemodialysis (HD) who were recruited from HD units in Ain Shams University Hospitals, Cairo, Egypt.

Study design

This is a cross-sectional study.

Inclusion criteria and subject selection

Age ≥ 18 and ≤ 60 years and clinically stable chronic HD patients on thrice-weekly 4-h sessions on HD for at least 6 months before the study were included.

Exclusion criteria

Diabetic patients; chronic liver disease patient's Child-Pugh class B or C; smokers; history of evident cardiac, peripheral, vascular, or cerebrovascular insult as transient ischemic attacks or strokes; uncontrolled hypertension; severe anemia (HB < 8 g/dl); collagen disease; and active infection were excluded from the study.

Patients on HD for at least 6 months before the study, using a standard bicarbonate-containing dialysate and using biocompatible HD membrane (Polysulphone, F6 series, Fresenius, Germany) low-flux dialyzer and heparin as an anticoagulant. Blood flow rates ranged from 250 to 300 mL/min, while dialysate flow rate was kept constant at 500 mL/min. All HD patients were maintained at their target dry body weight. A review of medical records included demographic data such as age, sex, smoking habits, body mass index (BMI) (kilograms/square meter), etiology of renal failure, duration of HD, vascular access, dry weight (kilograms), ultrafiltration (UF) volume (liters) on the session, the average of pre-HD systolic and diastolic BP (mmHg) per week, mean arterial BP (MAP; mmHg), concomitant medication, and biochemical test results were undertaken. Full general and neurological examination was done.

Laboratory measurements

Biochemical blood samples were collected before the midweek HD session and before heparin administration. Laboratory tests done for all patients included hemoglobin (Hgb), hematocrit, serum iron profile, creatinine, sodium (Na), potassium (k), blood urea nitrogen (BUN), calcium (Ca), phosphate (P), intact PTH (iPTH), albumin, lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), fasting blood sugar (FBS), and high-sensitivity CRP (hsCRP).

Urea reduction ratio (URR) was calculated using pre-dialysis urea (Upre) and post-dialysis urea (Upost). URR = Upre − Upost × 100/Upre.

All blood samples were collected pre-dialysis with the exception of the post-dialysis serum urea nitrogen to calculate urea kinetics. The HCV antibody status was examined using the third generation of HCV enzyme immunoassay

Transcranial Doppler sonography parameters

An assessment of cerebral circulation hemodynamics (for both sides) by transcranial Doppler sonography and transcranial color-coded duplex (DWL multidop x2, USA; esaote Mylab 5, Italy) using 2 MHz phased array probe insonating axial planes through temporal window while the patients are in the supine position was done. Patients were assessed in non-dialysis day to examine mean flow velocity (MFV) in the middle cerebral artery (MCA) and posterior cerebral artery (PCA). The MFVs in the MCA and PCA in our study were compared to normal according to Kassab et al. [5] as shown below:

- MFV of MCA: 55 ± 12 cm/s
- MFV of PCA: 40 ± 10 cm/s
- MFV of MCA is considered decrease when below 38 cm/s. MFV of PCA is considered decrease when below 29 cm/s

Extracranial carotid system (common carotid, internal and external carotid arteries) and vertebral artery (V0, V1, and V2 segments) for all subjects were assessed by carotid duplex using 5–12 MHz linear probe (esaote Mylab 5, Italy) to exclude extracranial stenosis, which may affect intracranial hemodynamics.

Ethics approval and consent to participate

This study was approved through the local ethics committee of Ain Shams University Hospital. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the enrolled patients have informed written consent. All patients or relatives were informed about the study and its possible benefits

Statistical analysis

The analyses were performed with Stata® version 11 for Windows (Stata Corp, College Station, TX, USA). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

1. Mean, standard deviation, and range for parametric numerical data.
2. Frequency and percentage of non-numerical data.

Analytical statistics

1- *Testing of normality of data* was done using Shapiro-Wilk test, and suitable statistical test was used accordingly whether the data follow the parametric or non-parametric distribution.
2- *Mann-Whitney test* (*U test*) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.
3- *Independent sample t test* was used to assess the statistical significance of the difference of a parametric variable between two independent means of two study groups.
4- *Chi-squared test* was used to examine the relationship between two qualitative variables but when the expected count is less than 5 in more than 20% of the cells; *Fisher's exact test* was used.
5- *Spearman's correlation coefficient* (*r*) will be used as a measure of the strength of a linear association between two quantitative variables. The correlation coefficient, *r*, can take a range of values from + 1 to − 1.
6- *Multiple Linear Regression analysis* was used to find out significant predictors of MCA and PCA scores.

Results

Patient baseline characteristics

Fifty HD patients (34 (68%) males and 16 (32%) females) with mean age 43 ± 10.56 year are included. The etiology of ESRD was hypertension in 30 (60%) of patients, obstructive uropathy in 5 (10%) patients, chronic glomerulonephritis in 5 (10%) patients, and 10 (20 %) patients with unknown etiology. Mean duration of dialysis was 71.36 ± 53.22 months, mean systolic BP 123.4 ± 14.23 mmHg, mean diastolic BP 79.8 ± 8.69 mmHg, and mean MAP 86.42 ± 10.12 mmHg, mean dry weight (kilograms) 73.5 ± 12.65, and mean ultrafiltration volume 2310 ± 761.91 ml/session in all patients with arterio-venous fistula as vascular access. Twenty-five of HD patients were HCV seropositive. Laboratory results were shown in Table 1. Antihypertensive medication taken by hypertensive patients was included in the study, including angiotensin-converting enzyme inhibitors, calcium channel blockers, and B-blockers at the time of the study. Studied patients were on maintenance dose of erythropoietin and vitamin D3 (alphacalcidol).

Table 1 Laboratory data of the studied patients

Studied parameters	Mean	SD
Urea pre (mg/dl)	138	33.42
Urea post (mg/dl)	52.3	16.20
URR (%)	61.33	9.69
Albumin (g/dl)	4.012	0.33
Ca (mg/dl)	8.03	0.84
PO4 (mg/dl)	5.156	1.57
iPHT (pg/ml)	859.214	505.3
FBS (mg/dl)	95.32	7.26
CRP titer (mg/dl)	8.34	5.33
HB (g/dl)	10.71	0.89
Cholesterol (mg/dl)	158.64	41.15
TG (mg/dl)	160.88	82.88
HDL (mg/dl)	42.44	8.04
LDL (mg/dl)	83.74	26.21

Cerebral blood flow velocities by transcranial Doppler

Assessment of cerebral circulation hemodynamics in non-dialysis day revealed the average MFV among studied patients in MCA was 57.44 cm/s and average MFVs in PCA was 37.4 cm/s. Sixteen (32%) of patients showed decrease MFV in MCA and 30 (60%) were normal. Regarding MFVs in PCA, 13 (26%) of the patients showed decrease MFVs, 33 (66%) were normal, and 4 (8%) of the patients failed due to poor bone window as shown in Table 2. Among patients with decreased MFV in MCA three patients had normal PCA MFV and 13 patients had also significant decrease in MFV of PCA.

Correlations

There was no significant correlation between MFV MCA or MFV PCA and age, dry weight, duration of hemodialysis, etiology of renal failure, ultrafiltration volume, pre-dialysis systolic and diastolic, or mean arterial BP ($P \geq 0.05$) in the present study. PCA mean velocity significantly decreases more in males than females ($\rho = -0.355$, $P = 0.015$).

URR% > 65% as one of the HD adequacy parameters was correlated significantly with MFV of MCA ($\rho = 0.337$, $P = 0.022$) by Spearman's correlation as shown in Fig. 1. Eleven HD patients with decrease MFV of MCA with URR < 65% and 5 patients with URR ≥ 65% were observed. There was a statistical significant correlation between PCA mean flow velocity and URR% ($\rho = 0.301$, $P = 0.042$) by Spearman's

Table 2 Descriptive parameters of transcranial Dopplerstudy inHD patients ($N = 50$)

Studied parameters	Mean	SD	Range
MCA (CM/SEC)	57.44	20.17	22.7–90
Normal	30		60%
Decreased	16		32%
Poor bone window	4		8%
PCA (CM/SEC)	37.47	11.26	20–63
Normal	33		71.74%
Decreased	13		28.26%

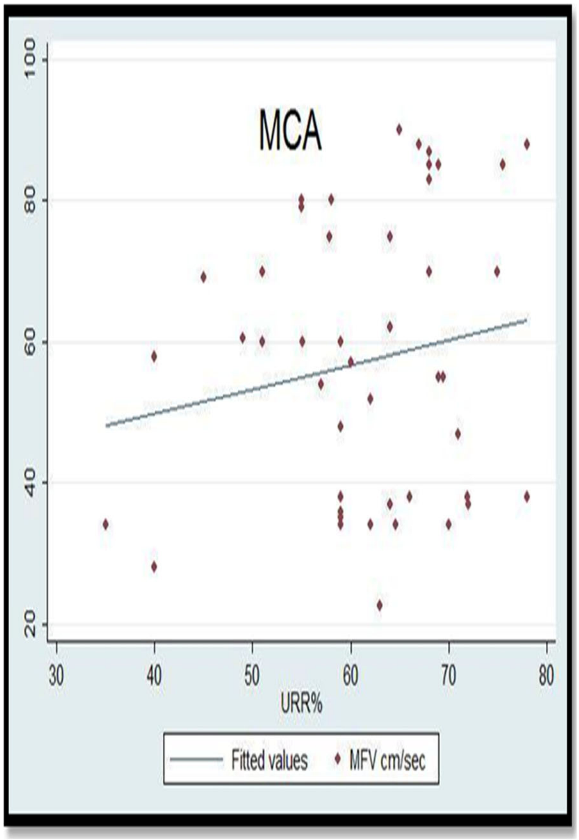

Fig. 1 Correlation between MCA score and URR% (*P* < 0.05)

correlation as shown in Fig. 1. As 10 (77%) patients of total HD developed a decrease in MFV of PCA had URR < 65%, 3 patients had URR ≥ 65%.

There was a significant correlation between PCA MFV and hemoglobin level (r = − 0.304, P = 0.039) (Fig. 2). But there is no statistically significant correlation of MCA or PCA MFV and other studied laboratory parameters as CRP titer, cholesterol level, TG, or serum albumin.

PCA MFV and MCA MFV were studied among HD patients with HCV seropositive in comparison to HD with HCV seronegative as there were no statistically significant differences as in HD patients with HCV seropositive MFV of MCA and PCA decreased by 9 (39%) and 83 (5%), respectively. In comparison to HCV seronegative group, MFV MCA and PCA decreased by 7 (30%) and 5 (22%), respectively.

Multivariate regression analysis of MCA as a dependent variable showed that URR value as independent factor affects the MCA mean flow velocity (adjusted β coefficient [95% CI] = 21.26 [8.67; 33.85], P = 0.002).

The URR value (adjusted β coefficient [95% CI] = 7.33 [0.52; 14.14], P = 0.036) and HB level (adjusted β coefficient [95% CI] = − 4.19 [− 7.72; − 0.65], P = 0.021) were

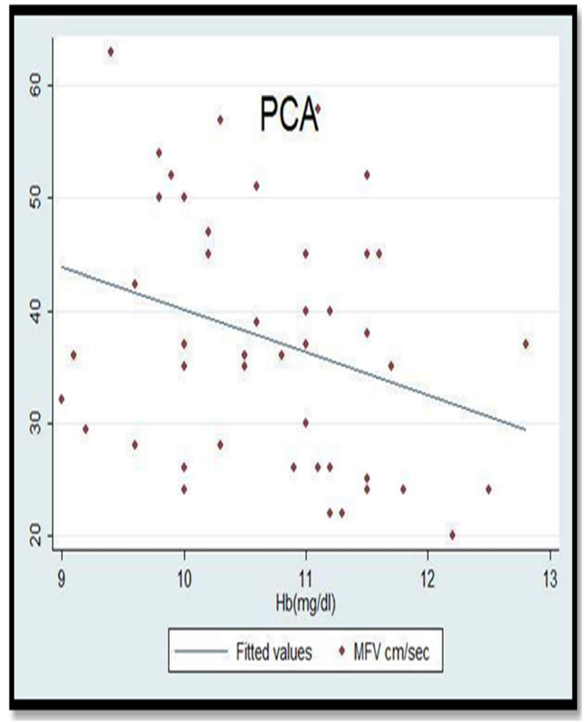

Fig. 2 Correlation between PCA score and hemoglobin level (*P* < 0.05)

independent factors affect PCV mean flow velocity significantly by multivariate regression analysis of PCA as dependent variable.

Discussion

The present study demonstrated a decrease in MFV of MCA and PCA by 32% and 28%, respectively, in non-dialysis day among non-diabetic ESRD on regular HD, which may carry high risk of increase prevalence of cerebrovascular stroke among HD patients

Previous studies observed cerebral blood flow changes during hemodialysis session that may be contributed to many intra-dialytic cycle factors as rapid volume ultrafiltration, transient hypotension, changes in electrolytes, and cerebral water content or arterial hypoxemia that may induce possible subtle brain damage [1, 6, 7]. Thus, the worst time to communicate with dialysis patients may be during the hemodialysis sessions [8].

The high frequency of decrease MFV of MCA or PCA, which assess the anterior and posterior cerebral circulation by transcranial Doppler in non-dialysis day away from hemodynamic changes occurred during HD session observed in this study, may be explained by premature atherosclerosis and endothelial dysfunction of the cerebral circulation among ESRD patients.

Urea reduction ratio (URR) is one of the HD adequacy parameters. In the current study, HD patients with URR more than 65% had a significantly higher median of MFVs than patients with inadequate dialysis (URR < 65%). So inadequate dialysis seems to be an important factor that contributes to the decrease of MFVs of MCA and PCA, as efficiently more removal of uremic toxins that attributed to endothelial dysfunction would result in maintaining cerebral perfusion. Other studies postulated that the usage of a high-flux dialyzer, nocturnal hemodialysis, or higher doses of hemodialysis in dialysis prescription to improve adequacy have better stabilization of cerebral hemodynamic [1].

There was a significant negative correlation between hemoglobin level and PCA MFV in the present study, as increase cerebral blood flow in response to hypoxia induced by decreased hemoglobin level. In agreement with previous studies that reported a mild reduction of velocity associated with a significant elevation of hemoglobin [9].

In the current study, we did not find a significant correlation between MFVs MCA or PCA and traditional atherosclerosis risk factors as cholesterol level, predialysis systolic, diastolic, or MAP. No significant correlation between cerebral blood velocities and albumin or CRP titer as markers of nutrition and inflammatory state

There is a hypothesis of the presence of chronic hepatitis C virus (HCV) infection as a cause of vascular disease with involvement of cerebral vessels through chronic inflammation effect as Cojocaru et al. in 2007 [10] reported that occlusive cerebral vascular diseases can also occur in the context of HCV-related vasculitis. Fletcher et al. [11] postulated that all of the *known HCV receptor molecules* present on the blood-brain barrier and HCV replication may be associated with cerebrovascular occlusion disorder. But we did not observed in the current study any statistically significant differences between HCV positive and HCV seronegative HD patients regarding MFV of both MCA and PCA.

However, some limitations could be noted in this study as the number of candidates studied was considered limited (small sample size). Also, there is a small number of females in comparison to the number of males which may be due to gender difference regarding renal failure.

Conclusion

There is a high frequency rate of decreased MCA and PCA MFV (32%, 28%), respectively, among non-diabetic prevalent hemodialysis patients with a significant correlation to hemodialysis adequacy. Hemodialysis patients should be assessed routinely using transcranial Doppler sonography as a screening test to detect early cerebral blood flow changes and for follow-up for further possible interventions to improve cerebral blood flow in those populations.

Abbreviations

ESRD: End-stage renal disease; MCA: Middle cerebral artery; MFV: Mean flow velocity; PCA: Posterior cerebral artery; TCD: Transcranial Doppler

Authors' contributions

MAB and AE conceived of the study and participated in its design and coordination and helped to draft the manuscript (FG). MS participated in the design of the study and performed the statistical analysis (ES). AES participated in the sequence alignment (MT). All authors read and approved the final manuscript.

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Availability of data and materials

Dataset is available as a master sheet in Excel format and publicly available in the Neurology Department, Ain Shams University, through communicating corresponding authors.

Ethics approval and consent to participate

The study was approved by Ain Shams University Ethical Committee in January 2016. Written informed consent was obtained from the patients participating in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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