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Association of plasma asymmetric dimethylarginine concentration changes with intradialytic hypotension and hypertension in chronic hemodialysis patients

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Abstract. Intradialytic hypertension and hypotension are both independently associated with increased morbidity and mortality among patients with chronic hemodialysis. Prior studies investigate the role of endothelial dysfunction in the mechanism of adverse intradialytic blood pressure changes. The aim of the current study was to investigate the association of plasma asymmetric dimethylarginine (ADMA), a marker for endothelial dysfunction, concentration changes pre-to-post-dialysis with both intradialytic hypertension and intradialytic hypotension. The study was a case-control study of 36 patients with chronic hemodialysis (12 patients in each group for intradialytic hypertension, intradialytic hypotension, and stable blood pressure). Intradialytic blood pressure changes were defined as increased or decreased systolic blood pressure pre-to-post-dialysis ≥ 10 mmHg in $\geq 4/6$ consecutive HD sessions. Dialysis resulted in significant reduction of the plasma ADMA concentration pre-to-post dialysis in each group ($0.26 \pm 0.15 \mu\text{mol/L}$, $p=0.00$ in patients with intradialytic hypertension; $0.18 \pm 0.15 \mu\text{mol/L}$, $p=0.01$ in patients with intradialytic hypotension; $0.17 \pm 0.09 \mu\text{mol/L}$, $p=0.00$ in patients with stable blood pressure). The reduction of plasma ADMA concentration in patients with intradialytic hypertension was significantly different compared to control group ($p=0.02$), albeit the insignificant difference in patients with intradialytic hypotension ($p=0.78$). Plasma ADMA concentration changes pre-to-post dialysis was considered as an insignificant risk factor ($\text{OR}=1.96$, $95\% \text{CI}$ [0.38-9.93, $p=0.41$]) for intradialytic hypertension.

1. Introduction

Hemodialysis (HD) is a procedure needed by most patients with end-stage renal disease (ESRD) to sustain life. It is estimated that there are more than 2 million patients with ESRD regularly receiving hemodialysis worldwide [1]. Lots of metabolic and hemodynamic alteration occur during HD, and consequently, patients undergoing HD may suffer from complications of HD acutely or chronically. Adverse blood pressure changes during hemodialysis are commonly observed in patients regularly receiving HD. Intradialytic hypertension is found in 15% patients with HD [2], while intradialytic hypotension is commoner, found in 20-30% patients with HD [3]. Some cohort studies report that increasing or decreasing blood pressure during hemodialysis is associated with increased hospitalization and premature mortality in patients with HD [4,5], thus signifying intradialytic hypotension and hypertension in the comprehensive management of patients with HD.

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There is no standard accepted definition of intradialytic hypertension or intradialytic hypotension presently, and thus the meticulous underlying mechanisms are still contentious [6]. Some studies report that intradialytic hypotension and hypertension are associated with endothelial dysfunction [7,8]. Increased concentration of asymmetric dimethylarginine (ADMA), a potent inhibitor of endothelial nitric oxide synthase, directly contributes to endothelial dysfunction. Zoccali et al report that ADMA concentration can predict morbidity and mortality in patients with ESRD [9]. To date, the study which relates the association between adverse blood pressure changes during hemodialysis and plasma ADMA concentration is lacking. The previous study conducted by Raj et al shows the insignificant difference among patients intradialytic hypertension, patients with intradialytic hypotension, and patients with stable blood pressure [10]. A recent study which explains the association between intradialytic pressure phenomena and mortality rates shows intradialytic blood pressure changes have important prognostic bearing [11]. We, therefore, opt to investigate the association of asymmetric dimethylarginine (ADMA) concentration changes pre-to-post-dialysis with both intradialytic hypertension and intradialytic hypotension.

2. Method

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The subjects were consecutively recruited from end-stage renal disease (ESRD) patients who regularly attended the session of HD in the Hemodialysis Unit of Mohammad Hoesin General Hospital Palembang. The prospective subjects were 18-60 years old and having regular HD for at least 3 months. Patients with uncompensated heart disease, sepsis, active gastrointestinal bleeding, and malignancy were excluded from the study. Patients were selected from a pool of 122 patients.

Table 1. General characteristics of the subjects.

Characteristics	Intradialytic Hypertension (n=12)		Stable Blood Pressure (n=12)		Intradialytic Hypotension (n=12)		P
	n	%	n	%	n	%	
Age (years)							0.91 ^a
24 – 36	2	16.7	1	8.3	1	8.3	
37 - 48	5	41.7	7	58.3	7	58.3	
49 – 60	5	41.7	4	33.3	4	33.3	
Sex							1.00 ^b
Male	7	58.3	7	58.3	7	58.3	
Female	5	41.7	5	41.7	5	41.7	
Body Mass Index (kg/m²)							0.75 ^a
< 18.5	3	25	1	8.3	1	8.3	
18.5– 22.9	7	58.3	7	58.3	7	58.3	
>23	2	16.7	4	33.3	4	33.3	
Cause of HD							0.47 ^b
Hypertension	12	100	7	58.3	1	8.3	
Diabetes Mellitus	0	0	3	25	1	8.3	
Renal Infection	0	0	1	8.3	9	75	
Intoxication	0	0	1	8.3	1	8.3	

^aOne-way ANOVA, ^bKruskal Wallis Test

Prior to the recruitment, the prospective subjects were followed in six HD sessions to determine the grouping of the subjects, whether the subjects were assigned to the group with intradialytic hypertension, intradialytic hypotension, or group with stable blood pressure. Intradialytic hypertension was defined as ≥ 10 mmHg increased of post-dialysis systolic blood pressure compared to pre-dialysis systolic blood pressure, on at least four of six sessions of HD, while intradialytic hypotension was defined as ≥ 10 mmHg decreased. The definition was based on the most-cited previous study which evinced intradialytic hypertension or hypotension as a predictor of premature mortality [10]. Stable blood pressure was defined as the < 10 mmHg alteration of blood pressure pre-and-post-dialysis on at least four of six sessions of HD. The blood pressure was measured ten minutes before each HD session and after the HD access removing while subjects were lying on the bed. The blood pressure was determined by the average value of two measurements with five minutes interval using mercury sphygmomanometer. Twelve matched subjects for each group was conducted in the study.

On the seventh HD session, body weight, pre-and-post-dialysis blood pressure, ureum, and ADMA was measured. ADMA was measured based on blood specimens which were drawn pre-and-post dialysis and was determined by enzyme-linked immunosorbent assay (ELISA). ADMA test kit used in this study was an enzyme immunoassay designed for direct quantitative determination of ADMA in biological fluids (AD 24 ELISA-Enzyme-Linked Immunosorbent Assay, ALPCO, Cat. No. 17-EA201x96, 12 × 8 test, DLD Diagnostika GMBH, H5nburg, Germany).

Normal distribution of data was deduced with the Kolmogorov-Smirnov test. Independent t-test and Mann-Whitney non-parametric test are applied to compare the significance of differences in interval variables if two groups of data were independent and dependent t-test and Wilcoxon non-parametric test was used to compare dependent samples. One-way ANOVA and Kruskal Wallis non-parametric test were used to compare data among more than two groups. P-values of less than 0.05 were considered to be significant. Statistical analysis was performed using SPSS 22.0 for Windows.

Table 2. Characteristic of subjects in seventh hemodialysis session.

Characteristics	Stable Blood Pressure (Control) (n=12)	Intradialytic Hypertension (n=12)	Intradialytic Hypotension (n=12)	
			P (Compared to Control)	P (Compared to Control)
Body Weight (kg)				
Pre-HD	59,29±11,49	56,46±10,20	0.16 ^a	56,00±11,60 0,45 ^a
Post-HD	56,05±11,39	53,86±10,17	0.22 ^a	53,29±10,17 0,53 ^a
Difference (post-pre)	3,23±0,84	2,58±1,26	0.00 [#]	2,71±0,79 0,00 [#]
Systolic Blood Pressure (mmHg)				
Pre-HD	140,13±23,16	151,66±18,76	0.08 ^a	157,50±22,62 0,00 [#]
Post-HD	139,86±26,77	169,30±18,10	0.00 [#]	140,97±20,15 0,97 ^a
Diastolic Blood Pressure (mmHg)				
Pre-HD	84,72±10,87	89,86±8,63	0.00 [#]	90,97±10,63 0,00 [#]
Post-HD	84,58±11,12	94,30±8,19	0.00 [#]	86,67±10,07 0,97 ^a
Duration of HD (months)	40,50±22,75	39,83±32,99	0.76 ^a	34,17±22,89 0,59 ^a
Blood Urea Nitrogen (mg/dl)				
Pre-HD	144,75±66,93	143,17±31,77	0.34 ^a	133,42±42,42 0,86 ^a
Post-HD	40,17±21,27	44,42±19,00	0.21 ^a	38,50±17,98 0,88 ^a
Difference (post-pre)	104,58±47,94	98,75±27,49	0.60 ^a	94,92±28,77 0,64 ^a
ADMA (u/M)				
Pre-HD	0,80±0,11	0,89±0,10	0.53 ^b	0,82±0,18 0,81 ^b
Post-HD	0,63±0,15	0,57±0,11	0.60 ^a	0,62±0,20 0,99 ^b
P value (pre-post)	0,00 [#]	0,00 [#]		0,01 [#]
Difference (post-pre)	0,17±0,09	0,26±0,15	0.02 ^c	0,18±0,15 0,78 ^b

HD: Hemodialysis; ^aMann-Whitney Test; ^bIndependent T-test; ^cDependent t-test; #p<0.05 is considered to be significant.

3. Results

There were 36 patients recruited in total and there were any patients excluded from the study. General characteristics of subjects were shown in Table 1. Most of the patients were normoweight and were between 37-years-old and 48-years-old. There were 21 males and 15 females. The commonest etiology of HD was hypertension. The characteristics were insignificantly different among groups

The measurements in the seventh HD session were shown in table 2. The body weight changes pre-to-post dialysis were significantly higher in the control group compared to both intradialytic hypertension and intradialytic hypotension group. There was no significant difference in the duration of HD and blood urea nitrogen among groups. Dialysis resulted in significant reduction of the plasma ADMA concentration pre-to-post dialysis in each group. The reduction of plasma ADMA concentration in patients with intradialytic hypertension was significantly different compared to the control group.

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To measure the association between plasma ADMA concentration and the incidence of intradialytic hypertension, the cutoff value was shown in figure 1. The cutoff value was 0.19 $\mu\text{mol/L}$ with sensitivity and specificity which were 58%. The chi-square table was shown in table 3.

4. Discussion

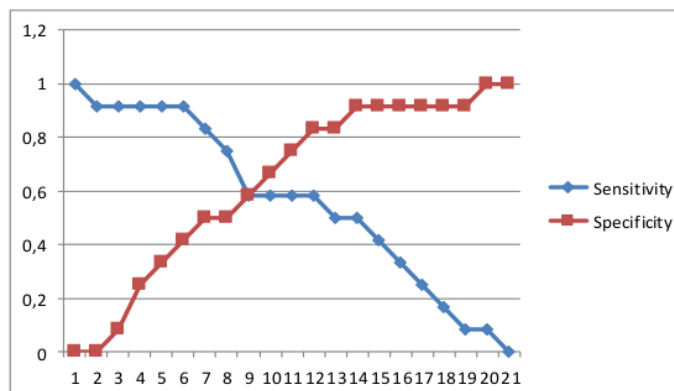
Asymmetric dimethylarginine (ADMA), which is an amino acid of 202 Da, is an endogenous competitive inhibitor of nitric oxide synthase [12]. Its action reduces the generation of nitric oxide (NO) thus impeding the advantageous functions of NO on vasodilatation, arterial elasticity, and endothelial function [13]. Increased plasma ADMA concentration has been associated with CV events and death in patients receiving hemodialysis [9]. In patients with ESRD, plasma ADMA concentration is higher compared to patients with normal renal function [14]. Increased plasma ADMA concentration in the circulation is a combined result of decreased renal function and impaired catabolic activity of dimethylarginine dimethylaminohydrolase [15]. Patients with ESRD treated by hemodialysis are having the highest elevation of plasma ADMA concentration compared to other conditions with impaired renal function. It is estimated that 60% of ADMA is removed from plasma during a hemodialysis session [16].

The current study investigated the association of plasma ADMA concentration changes pre-to-post dialysis with intradialytic hypertension and intradialytic hypotension in patients with chronic HD. The current study found that the dialysis reduced the plasma ADMA concentration. The similar result was also found on the previous study [10]. This finding supports the theory that ADMA is removed from plasma during hemodialysis session [16].

Table 3. Asymmetric dimethylarginine (ADMA) concentration change in intradialytic hypertension group compared to control group.

ADMA Concentration Change	Intradialytic Hypertension (n)	Stable Blood Pressure (n)	OR[95%CI, p value]
(>0.19)	7	5	1.96 [0.38-9.93,
(<0.19)	5	7	p=0.41]

Figure 1. Cut off point for asymmetric dimethylarginine (ADMA) concentration change in intradialytic hypertension group.



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The current study identified that mean plasma ADMA concentration reduction was higher in patients with intradialytic hypertension, compared to patients with stable blood pressure, albeit the insignificant difference between patients with intradialytic hypotension and patients with stable blood pressure. The different result was shown in the previous study conducted by Raj et al [10] which found there is no significant difference among groups. The different results might be caused by the different definition of intradialytic adverse blood pressure changes. Raj et al defined intradialytic hypertension and hypotension as increased mean arterial pressure (MAP) ≥ 15 mm Hg from baseline during HD and decreased mean arterial pressure (MAP) ≥ 15 mm Hg from baseline during HD, respectively. The

current study used the newer perspective that linked the definition to the important prognostic bearing. These findings suggested the role of ADMA in regulating intradialytic blood pressure on patients with chronic HD whose mortality increased with intradialytic hypertension.

5. Conclusion

In conclusion, the current study proposed that plasma ADMA concentration changes pre-to-post-dialysis may partially explain the higher event rates observed in patients with intradialytic blood pressure changes. Although plasma ADMA concentration changes pre-to-post dialysis was considered as an insignificant risk factor for intradialytic hypertension, the current study supported the proposed theory of endothelial dysfunction in intradialytic hypertension. Further studies required in larger sample size to confirm the higher ADMA concentration reduction as a clinical risk factor for intradialytic hypertension.

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