IJKD DIALYSIS

Ambulatory Blood Pressure Monitoring in Hemodialysis Patients with Intradialytic Hypertension

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Keywords. blood pressure monitoring, ambulatory, hemodialysis, hypertension

Introduction. It has not yet been clear whether intradialytic hypertension (IDHN) translates into the presence of high BP between dialysis sessions or not. In this study, we aimed to perform interdialytic ambulatory blood pressure monitoring (ABPM) in patients with IDHN to find whether high BP persists at home.
Methods. In this case-control study, ABPM was performed during a 44-hours interdialytic period in patients on maintenance hemodialysis (HD) with pre-dialysis systolic BP (SBP) above 130 mmHg. Bland-Altman graphs were used to investigate the magnitude of the difference between the results of ABPM records and intradialytic BP measurements in patients with and without IDHN.
Results. A total of 56 patients were enrolled in our study (29 in the IDHN group and 27 in the control group). The average of the pre-dialysis SBP in 6 consecutive HD treatments was 146.6 ± 11.36 vs. 146.8 ± 12.1 mmHg in IDHN and control group, respectively ($P > .05$). Mean post-dialysis SBP was 154.45 ± 12.6 mmHg in the IDHN group and 136.76 ± 11.50 in the control group ($P < .001$). Mean ± SD of 44-hour SBP was 157.31 ± 20.27 mmHg in the IDHN group, which was significantly higher than that in the control group (146.5 ± 16.67 mmHg, $P < .05$). No significant differences were seen in the average of interdialytic weights gain between the two groups. Compared to the pre-dialysis SBP, using Bland-Altman graphs, the post-dialysis SBP (bias of 3.5 mmHg) had closer readings to the daytime SBP in the IDHN group.
Conclusion. Patients with IDHN had higher interdialytic BPs. Among BPs taken during HD in patients with IDHN, post-dialysis SBP had the lowest difference with the daytime SBP taken by ABPM.

IJKD 2020;14:126-32
www.ijkd.org

Original Paper

INTRODUCTION

Hypertension, which is a common finding in patients with end-stage renal disease (ESRD), is associated with increased cardiovascular morbidity and mortality.[1] Several studies have reported hypertension to be prevalent in over 60% of patients undergoing hemodialysis (HD).[2,3] Due to lack of randomized trials, the target ranges of blood pressure (BP) in this population have not been well-established and have been mostly based on studies conducted on patients not undergoing HD. Additionally, it has not yet been clear whether BPs taken during HD, i.e. the immediate pre- and post-dialysis measures, reflect the mean interdialytic BP, particularly in those with intradialytic hypertension (IDHN).[4,5] IDHN, which is defined as more than 10 mmHg increase in the systolic BP from the immediate pre- to post-

HD, is associated with short-term and long-term risks.[5-8] It has not been well clear whether patients with IDHN have high BPs at home. Continuous monitoring of BP, i.e. ambulatory BP monitoring (ABPM), is the gold standard method to evaluate interdialytic BP and the associated risk of adverse events; however, its cost and lack of patient cooperation are limiting factors.[5] The fluctuating nature of BP and excessive variations in volume status of patients undergoing HD have made 44-hours ABPM more accurate than a 24-hours one in predicting organ damage and determining the prognosis of patients undergoing HD.[9] Few studies have investigated the status of home BP in patients with intradialytic hypertension. It is not well known whether IDHN translates into the presence of high BP between dialysis sessions.

In this study, we aimed to compare the result of 44-hour interdialytic ABPM between patients with and without IDHN to find whether high BP persists at home in patients with IDHN.

MATERIALS AND METHODS

To select eligible patients, ESRD patients on chronic maintenance HD at three HD centers, affiliated with Shiraz University of Medical Sciences, were screened. Fifty-six patients aged at least 18 years with at least one month on regular thrice-weekly 4-hour HD were found eligible for the study. We included those who had achieved dry weight clinically and had pre-dialysis systolic BP (SBP) above 130 mmHg. Using polysulfone dialysis membranes, HD was performed for 4 hours using bicarbonate dialysate, with a dialysate potassium concentration of 2 mEq/L. Patients with active infection or malignancy, obvious signs of volume overload, and with any change in the dose of antihypertensive drugs or erythropoietin stimulating agents during the month prior to the enrollment were excluded from the study. The patients were categorized into two groups: IDHN group (rise of SBP from pre- to post-HD of at least 10 mmHg in at least four out of the six HD treatments) and control group (drop in SBP from pre- to post-HD treatment of at least 10 mmHg in at least four out of the six HD treatments). Immediate pre- and post-HD BP were measured by mercury sphygmomanometers (Riester, Germany) for 6 consecutive HD sessions from the non-access arm brachial artery after 5-minute rest in a sitting position. Other information such as age, sex, duration of HD, underlying etiology of ESRD, and anti-hypertensive drugs consumption was recorded.

All the patients signed the written informed consent before the enrollment. The Ethics Committee of Shiraz University of Medical Sciences approved the study protocol. Pre- and post-HD weights were measured at a standing position, before and after HD, and recorded in kilograms. Pre- and post-HD weight, just before and after ABPM, was measured to assess interdialytic weight gain. Interdialytic weight gain was defined as the difference between the pre-HD weight and the immediate post-HD weight. The BP of six HD treatments before ABPM was averaged for both SBP and diastolic BP (DBP). After a midweek HD treatment, the patients with the above criteria were considered for ABPM from the non-access arm by a trained nurse. After the device (Sun Tech 222, USA) was turned on and the first measurement was performed, the patient left the HD unit for a 44-hour interdialytic period. BP was measured every 30 minutes during awaking at the beginning of the day and every 1-hour during sleeping at night (the period of awakening and night sleep was individualized for each person and set by the device). During this period, the patients continued their anti-hypertensive drugs and their usual diet and activity. Just before starting the next HD treatment, the ambulatory ABPM device was turned off and picked up by a trained nurse. In patients with incomplete recording, the procedure was repeated in the next week.

Statistical Analysis

Descriptive data were reported as mean ± standard deviation (SD) and categorical variables as percentage. Comparisons between the groups were performed by t-test for continuous variables and chi-square test for categorical variables. $P < .05$ was considered statistically significant. To investigate the magnitude of the difference between the results of ABPM records and intradialytic BP measurements, Bland-Altman graphs were drawn. Bland-Altman graphs are usually used to assess the agreement between the measured parameters or to compare a measurement method to the gold standard method. This graph presents a picture of the difference between the measurements obtained by the two methods versus the means of these measurements. Less difference between the methods makes the

obtained points on the graph (or mean differences) closer to the zero horizontal line. Calculation of the Bland-Altman limits of agreement identifies the observations falling outside this range as observations with disagreement between the two methods. Statistical analysis was conducted by the statistical software SPSS 18 (SPSS Inc., Chicago, IL).

RESULTS

Demographic Characteristics

Of the 56 patients, 29 had IDHN and 27 did not have IDHN (control group). The patients in the IDHN group had the mean ± SD age of 52.31 ± 11.3 years of which 20 (69%) were male. As Table 1 shows, the average age and the sex distribution of the two groups were similar ($P > .05$ and $P > .05$, respectively). Total time on the HD treatment was 28.34 months in the IDHN group and 38.5 months in the control ($P > .05$).

Table 1 shows the prevalence of diabetes and hypertension as a cause of ESRD. The mean ± SD number of antihypertensive drugs per patient was 2.1 and 1.4 in IDHN and control groups, respectively ($P < .05$). Table 1 presents the distribution of the different categories of antihypertensive drugs; other than the alpha blockers, no significant difference was found between the two groups. Dialysate concentrations of sodium, potassium, bicarbonate, and calcium and dialysate flow rate were the same in all patients. The mean blood flow rates were 265.17 mL/min and 263.52 mL/min in IDHN and control groups, respectively ($P > .05$). No significant differences were seen in the average of ultrafiltration volumes, interdialytic weights gain, and dialysis adequacy (by Kt/V) between the two groups (Table 1).

Table 1. Demographic and Baseline Characteristics of the Study Subjects

Patients' Characteristics	Intradialytic Hypertension Group (n = 29)	Control Group (n = 27)	*P*
Age, year	52.31 ± 11.3	48.8 ± 11.5	> .05
Male, %	20 (69)	15 (55.5)	> .05
BMI, kg/m^2	24.4 ± 3.6	23.6 ± 4.7	> .05
Diabetes, %	11 (37.9)	6 (22.2)	> .05
Number of Antihypertensive Drugs Per Patient	2.17	1.44	< .05
Anti-hypertensive Drugs (%)	26 (89.7)	21 (77.8)	> .05
Calcium channel blockers, %	18 (62.1)	15 (55.6)	> .05
Beta blockers, %	14 (48.3)	10 (37.0)	> .05
Alfa blockers, %	15 (51.7)	7 (25.9)	< .05
ARBs, %	8 (27.6)	3 (11.1)	> .05
ACEIs, %	1 (3.4)	0 (0.0)	> .05
Direct Vasodilators, %	2 (6.9)	0 (0.0)	> .05
Central Alfa Agonists, %	2 (6.9)	1 (3.7)	> .05
Diuretics, %	3 (10.3)	3 (11.1)	> .05
Use of ESA, %	22 (75.9)	16 (59.3)	> .05
Calcitriol Use, %	9 (31.0)	12 (44.4)	> .05
Laboratory Parameters			
Hemoglobin, g/dL	11.18 ± 1.81	11.73 ± 1.29	> .05
Serum BUN, mg/dL	60.83 ± 16.06	59.67 ± 18.67	> .05
Serum Creatinine, mg/dL	7.97 ± 2.12	8.53 ± 2.82	> .05
Serum Calcium, mg/dL	8.52 ± 0.71	8.36 ± 0.81	> .05
Serum Phosphorus, mg/dL	4.92 ± 1.41	5.40 ± 1.58	> .05
Serum Albumin, g/dL	3.77 ± 0.37	3.98 ± 0.49	> .05
Serum Potassium, mEq/L	5.56 ± 0.75	5.57 ± 0.71	> .05
Serum 25-hydroxy Vitamin D, pg/dL	19.81 ± 12.69	16.75 ± 9.57	> .05
Serum Parathyroid Hormone, pg/dL	415.04 ± 492.31	496.73 ± 284.26	> .05
Ultrafiltration Volume, L	2.68	2.73	> .05
Inter-dialytic Weight Gain, kg	2.32	2.48	> .05
Blood Flow Rate, mL/min	265.17	263.52	> .05
KT/V	1.32 ± 0.22	1.40 ± 0.14	> .05

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESA, erythropoietin stimulating agents

HD Unit BPs

The mean ± SD pre-dialysis SBP and DBP in 6 consecutive HD treatments were 146.6 ± 11.36 vs. 146.8 ± 12.1 mmHg and 81.4 ± 6.3 vs. 79.19 ± 5.1 mmHg in IDHN and control groups; respectively ($P > .05$ and $> .05$, Table 2). Mean ± SD post-dialysis SBP and DBP were 154.45 ± 12.6 mmHg and 85.05 ± 6.45 mmHg in the IDHN group and 136.76 ± 11.50 and 74.93 ± 4.17 mmHg in the control group ($P < .001$ for SBP and DBP). The mean HD unit SBP (the average of all post- and pre-HD SBP measurements) in 6 HD treatments was 151.57 mmHg in patients with IDHN and 141.78 mmHg in the control group ($P \leq .001$).

ABPM Results

As Table 2 depicts, the average 44-hour SBP in the IDHN group was 157.31 ± 20.27mmHg, which was significantly higher than that in the control group with 146.5 ± 16.67 mmHg ($P < .05$). The daytime and overnight SBPs were also significantly higher in the IDHN group than in the control group (159.9 ± 20.7 vs. 147.4 ± 15.8 mmHg, $P < .05$ for the daytime and 160.55 ± 21.9 vs. 144.8 ± 15.1 mmHg, $P < .05$ for overnight). No patient in both groups had normal nocturnal dipping in BP (decrease in the mean nocturnal SBP of at least 10% from the daytime SBP).

The Difference Between ABPM Measurements and HD Unit BP Recordings

To show the amount of disagreement between HD unit BP reading and ABPM measurements, the difference between the daytime SBP measured by 44-hours ambulatory monitoring and SBP measured during HD sessions was calculated in both groups. As Table 3 presents, the daytime SBP in the IDHN group had no significant difference with post-dialysis SBP (mean difference: 3.5 mmHg, 95% CI: -1.2 - 8.1; $P > .05$). However, in the control group, pre-dialysis SBP had closer readings to the daytime ambulatory SBP (mean difference: 0.5 mmHg, 95% CI: -2.6 - 3.6; $P > .05$, Table 3). As Bland-Altman graphs demonstrated (Figure), the average of the daytime ambulatory SBP measurements and HD unit SBPs was plotted versus the mean differences between them. In the IDHN group (Figure A), post-dialysis SBP had less difference [bias of 3.5 mmHg (± 2SD: -20.7, 27.2)] with and closer reading to the daytime SBP than pre-dialysis and mean HD unit SBP. However, in the control group (Figure B), it was the pre-dialysis SBP, rather than

Table 2. Ambulatory and intradialytic blood pressure recordings in patients with intradialytic hypertension versus controls

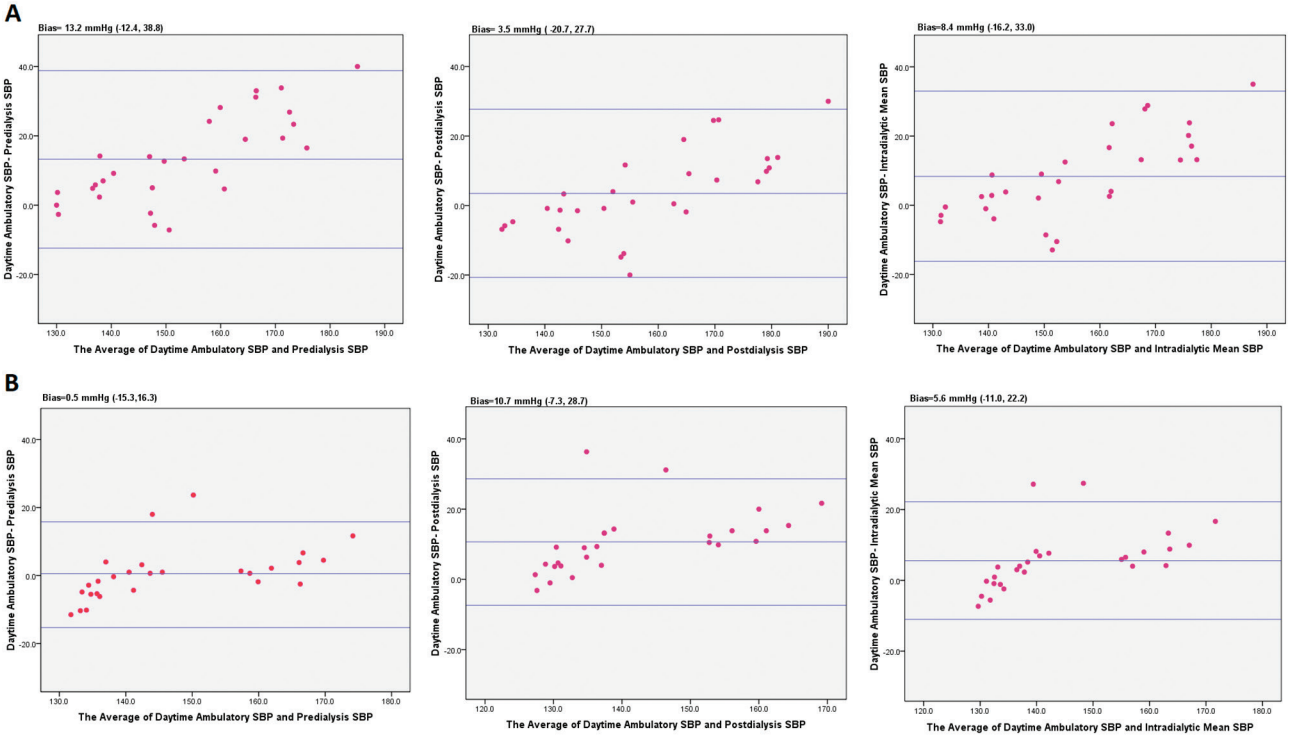
Blood Pressure Measurements	Intra-dialytic Hypertension Group (n = 29)	Control Group (n = 27)	*P*
Total 44h Ambulatory SBP, mmHg	157 ± 20.2	146 ± 16.6	< .05
Total 44h Ambulatory DBP, mmHg	80.9 ± 10.3	80.7 ± 10.4	> .05
Daytime Ambulatory SBP, mmHg	159.9 ± 20.7	147.4 ± 15.8	< .05
Daytime Ambulatory DBP, mmHg	82.2 ± 11.04	81.3 ± 10.7	> .05
Nocturnal Ambulatory SBP, mmHg	160.55 ± 21.9	144.8 ± 15.1	< .05
Nocturnal Ambulatory DBP, mmHg	82.7 ± 10.2	79.5 ± 10.5	> .05
Mean Percent of Nocturnal SBP Dipping, %	-0.37	1.5	> .05
Average of Pre-dialysis SBP (in 6 sessions)	146.6 ± 11.36	146.8 ± 12.1	> .05
Average of Pre-dialysis DBP (in 6 sessions)	81.6 ± 6.3	79.19 ± 5.10	> .05
Average of Post-dialysis SBP (in 6 sessions)	156.4 ± 12.6	136.7 ± 11.5	< .001
Average of Post-dialysis DBP (in 6 sessions)	85.05 ± 6.4	74.9 ± 4.17	< .001

DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 3. The Difference Between the Daytime SBP Measured by 44-hour Ambulatory Monitoring and the SBP Measured During Dialysis Sessions

Groups	Intra-dialytic Hypertension Group			Control Group		
Variables	Mean Difference	95% CI	*P*	Mean Difference	95% CI	*P*
Daytime vs. Pre-dialysis SBP, mmHg	13.2	8.4 - 18.1	< .001	0.5	–2.6 - 3.6	> .05
Daytime vs. Post-dialysis SBP, mmHg	3.5	–1.2 - 8.1	> .05	10.7	7.1 - 14.2	< .001
Daytime vs. Mean HD Unit SBP, mmHg	8.4	3.7 - 13.0	< .05	5.6	2.3 - 8.9	< .05

Abbreviations: CI, confidence interval; SBP, systolic blood pressure



Bland–Altman plots demonstrates the difference between daytime ambulatory systolic blood pressure (SBP) measurements and SBP measured during dialysis sessions. The upper panels (A) belong to the IDH group, and the lower panels (B) demonstrate the results for the control group.

post-dialysis or mean HD unit SBP, which had the lowest difference with the daytime SBP [bias of 0.5 mmHg (± 2SD: -15.3, 16.3)].

DISCUSSION

Hypertension as a common finding among the patients with ESRD has been linked to cardiovascular morbidity and mortality in these patients. Measurement and evaluation of BP are usually performed in the HD unit; however, measurement of BP in the HD unit is not a good indicator of interdialytic BP control.[10] Studies have indicated that rise of BP during HD, i.e, IDHN, has been linked to higher mortality rate.[11] It has not been clear whether they are hypertensive at home or not and whether they need higher doses of anti-hypertensive drugs compared to those who do not experience that rise in BP during HD.

Our study showed that in patients with IDHN, the average 44-hours and the daytime as well as the night-time SBP were significantly higher despite almost similar immediate pre-dialysis SBP and the same amount of interdialytic weight gain. Furthermore, the patients in the IDHN group took a higher number of anti-hypertensive drugs. Therefore, immediate pre-dialysis SBP could not be considered a reliable index to estimate the need for or escalate the dose of antihypertensive medications in patients with IDHN. In one study conducted by Van Buren at Texas University in 2011,[4] it was indicated that 44-hours SBP as well as pre-dialysis SBP were higher in the IDHN group than in the control group. They also demonstrated that the post-HD BP rise in patients with IDHN was not transient, and in contrast to the control group who had a persistent elevation of BP, they experienced a decreasing trend in the first 24 hours after HD. Our study resulted in the same finding but in a slightly different way. We included patients undergoing HD with pre-dialysis SBP higher than 130, which was lower than that of the mentioned study. Moreover, in contrast to the mentioned study in which the pre-dialysis SBP was higher in the IDHN group, SBP before HD was almost similar in both groups in our study.

In the previously mentioned study, ABPM indices were more correlated with the post-dialysis SBP in the IDHN group, being consistent with the present study results but in a different way. We used the Bland-Altman graphs to illustrate the

magnitude of the difference between the results of ABPM and the SBPs recorded during HD. As the Bland-Altman graphs showed, there was a bias, i.e. mean difference, of nearly 3.5 mmHg between post-dialysis SBP and the daytime ABPM SBP readings considering that most of the readings were in the range of ± 2SD (-20.7, 27.7) of the mean difference. However, as the post-dialysis SBP increases, the difference becomes wider, indicating that management of hypertension according to ABPM indices is more accurate than HD unit BPs, the conclusion which is in agreement with other studies.[10,12,13] It is not yet clear whether interventions aiming at minimizing the rise of BP during HD could reduce home BP in patients with IDHN. The underlying mechanism of IDHN is not yet clear, and there is a small amount of data about the role of renin angiotensin aldosterone system.[14] Endothelial cells dysfunction as well as the changes in the balance of endothelin-1/nitric oxide have been proposed to be the underlying mechanisms of IDHN.[14,15] Although volume overload has been mentioned as one of the potential causes of intradialytic hypertension, bio-impedance analysis was not available to analyze the volume status of the study subjects. Not only none of our patients had obvious signs of volume overload, but also the extent of interdialytic weight gain and the amount of ultrafiltration volume were not significantly different in the two groups. Using bio-impedance analysis, there are studies, which found higher extracellular volume status in patients with IDHN than others.[16] In one *post hoc* analysis of the dry weight reduction in hypertensive hemodialysis patients (DRIP) trial, Agarwal examined the hypothesis that intradialytic changes in BP indicated excess volume and concluded that IDHN might be a sign of volume overload.[17] Interestingly, in both groups, none of the patients were night dippers, i.e. 10% decrease in nocturnal systolic BP. This is in accordance with the previous similar study mentioned.[4] Renin angiotensin aldosterone activity, sympathetic activity, volume overload and uremic neuropathy have been proposed to be the cause of non-dipping. Sleep disorders and inactivity during the day in patients undergoing dialysis are other causes.[18] One of the limitations of the present study was the method by which HD units BPs were measured, by a mercury sphygmomanometer. If we could use digital devices, then the measurements would have not been dependent on the nurses. The definition of IDHN presented in the current study was according to the previous studies; therefore, the lack of a standard definition for IDHN was another limitation of our study.[4,7,8] Hourly measurements of BP during HD, rather than only two measurements at the start and the end of HD, would have been more helpful and better correlated with ABPM measurement. Although the amount of intradialytic weight gain was not significantly different between the two groups, it did not necessarily translate to equal amount of fluid overload. Therefore, the lack of measurement of body fluid compartments and accurate evaluation of extra cellular fluid volume was another limitation of the present study. We did not lower the dry-weight; therefore, we cannot state whether IDHN is causally related to volume excess or not.

CONCLUSION

In conclusion, our study demonstrated that ESRD patients with IDHN had higher home BPs between dialysis sessions i.e. higher levels of interdialytic BPs. Among BPs taken during HD, post-HD SBP had the least bias with the daytime ABPM in patients with IDHN. Therefore, pre-HD BP, which is usually taken immediately before starting an HD session, is not a good indicator of interdialytic BP status in patients with IDHN.

ACKNOWLEDGMENTS

This research was financially supported by Shiraz University of Medical Sciences under grant number 93-01-49-7197. This article is a part of a thesis to be submitted by Maryam Shafiee for the degree of Subspecialty in Nephrology at Shiraz University of Medical Sciences.

DISCLOSURE STATEMENT

The authors declare that there are no disclosure statements.

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Received August 2019
Revised October 2019
Accepted January 2020