Original Article

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The Association Among Post-hemodialysis Blood Pressure, Nocturnal Hypertension, and Cardiovascular Risk Factors

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Background: Most hemodialysis (HD) patients suffer from hypertension and have a heightened cardiovascular risk. While blood pressure (BP) control is essential to end-stage kidney disease (ESKD) patients, overly stringent control can lead to intradialytic hypotension (IDH). This study aimed to examine BP variations during and after HD to determine whether these variations correlate with IDH risk.
Methods: BP measurements during dialysis were taken from 28 ESKD patients, and ambulatory BP monitoring was applied post-dialysis. Laboratory parameters and risk factors, including diabetes, coronary disease, and LV mass index, were compared between IDH and non-IDH groups using an independent t-test.
Results: Of the 28 patients with an average age of 57.4 years, 16 (57.1%) had diabetes, 5 (17.9%) had coronary artery disease, and 1 (3.6%) had cerebrovascular disease. The mean systolic blood pressure (SBP) during and post-HD was 142.26 mmHg and 156.05 mmHg, respectively (p=0.0003). Similarly, the mean diastolic blood pressure (DBP) also demonstrated a significant increase, from 74.59 mmHg during HD to 86.82 mmHg post-HD (p<0.0001). Patients with IDH exhibited a more substantial SBP difference (delta SBP, 36.38 vs. 15.07 mmHg, p=0.0033; age-adjusted OR=1.58, p=0.0168) and a lower post-dialysis BUN level (12.75 vs. 18.77 mg/dL, p=0.0015; age-adjusted OR=0.76, p=0.0242). No significant variations were observed in daytime and nocturnal BP between the IDH and non-IDH groups.
Conclusion: Hemodialysis patients exhibited a marked increase in post-dialysis BP and lacked a nocturnal BP dip, suggesting augmented cardiovascular risks. This highlights the importance of more stringent BP control after hemodialysis.

Key Words: Ambulatory blood pressure, End-stage kidney disease, Hemodialysis, Hypertension, Nocturnal hypertension

INTRODUCTION

Life expectancy has risen due to better control over infectious diseases and acute cardiovascular conditions, leading to an increased number of chronic illnesses such as diabetes and hypertension. Additionally, as patients with diabetes and hypertension age, the incidence of end-stage kidney disease (ESKD) also rises[1)]. Although advancements in dialysis treatment have improved survival rates for ESKD[2)], these patients still have significantly lower survival rates than the general population, primarily due to cardiovascular complications[3)].

Hypertension, following diabetes, is the second most common cause of ESKD, and its severity correlates with a decreased glomerular filtration rate. As renal function deteriorates, patients often become hypertensive, and most of

those undergoing dialysis suffer from hypertension[4]. Factors such as vascular stiffness and autonomic dysfunction also contribute to fluctuations in blood pressure (BP) among dialysis patients[5]. While regulating the BP of hemodialysis patients is crucial, stringent BP control during dialysis treatments can result in intra-dialytic hypotension (IDH), leading to potential vascular access thrombosis[6]. Notably, there's a U-shaped relationship between BP and mortality in dialysis patients, emphasizing the importance of proper BP regulation in dialysis environments[7]. While Ambulatory blood pressure monitoring (ABPM) is an effective diagnostic tool for hypertensive patients[8], its application is limited in hemodialysis patients due to compliance issues and constraints related to the use of the arteriovenous fistula arm.

In this study, we examined BP changes during and post-hemodialysis, including nocturnal BP variations using ABPM, to determine the relationship between BP fluctuations and the cardiovascular risks in ESKD patients.

METHODS

1. Patients

From Sep 1st, 2019, to Aug 31, 2020, we prospectively enrolled ESKD patients at Chungbuk National University Hospital who had undergone hemodialysis for at least 3 months, were >19 years of age, had hypertension (>140/90 mmHg), took anti-hypertensive medication, and agreed to undergo a 24-hour BP measurement. We excluded patients with acute illnesses, those who had been admitted to a hospital within the past 6 months, those with cancer, and those with uncontrolled anemia (Fig. 1). All patients continued taking their anti-hypertensives, and adjustments were made by clinicians based on BP changes. IDH was defined as a required systolic blood pressure (SBP) or diastolic blood pressure (DBP) decline of >20 mmHg during hemodialysis sessions on the day of the ABPM check. Delta SBP and DBP were defined as the differences between the highest and lowest values recorded during dialysis treatment or ABPM. This research was approved by the Institutional Research Board (IRB) of Chungbuk National University Hospital (IRB No: 2020-03-039). We included only participants who provided informed consent.

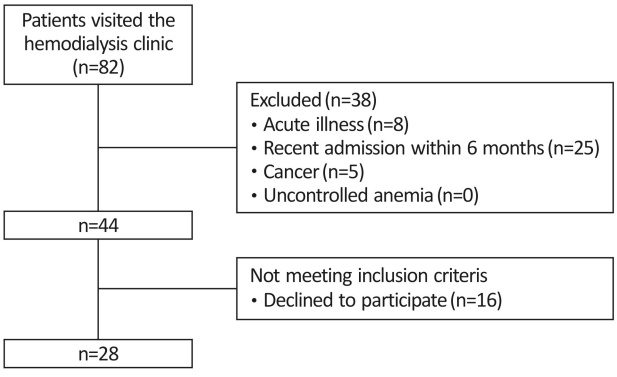

Fig. 1. Flow diagram of the patient selection.

2. Hemodialysis and BP Analysis

Hemodialysis sessions lasted 4 hours each and were conducted thrice a week. The morning sessions were scheduled from 08:30-09:00 to 12:30-13:00, while the afternoon sessions took place from 13:00-13:30 to 17:00-17:30. We utilized the Artis Physio dialysis machine by Baxter (USA) and the 5008S machine from Fresenius Medical Care (Germany). Dialyzers employed included Theranova 400 (Baxter, USA) and FX-100 (Fresenius Medical Care, Germany), matched to their respective manufacturers. Blood pressure was monitored hourly during each session. As per clinical guidelines, the patients' target blood pressure was set at 140/90 mmHg before dialysis and adjusted to 130/80 mmHg post-dialysis.

3. 24-Hour BP Monitoring

Ambulatory BP was measured using the TM-2430 ABPM kit (A&D company, Japan). At the end of the dialysis session, we applied a portable BP cuff and compared BP with those of the dialysis machine. All the patients were educated to keep the ABPM for at least 24 hours post-dialysis. The collected ABPM data were transferred to a desktop in the hemodialysis unit for analysis. Daytime BP readings, which included the dialysis period, spanned from 6:00 a.m. to midnight. Nocturnal BP readings were taken from midnight to 6:00 a.m. using the ABPM kit.

4. Blood Test and Echocardiography

All patients underwent routine laboratory tests in the dialysis unit every month. Chest X-rays were performed every

three months. Additionally, patients received echocardiography at least once every two years, which included assessments of the left ventricle (LV) ejection fraction and LV mass index. Medications for phosphorus, potassium, and anemia were adjusted monthly.

5. Statistical Analysis

All data are presented as mean ranges. The paired t-test was employed to compare BP during dialysis with home BP. Patients with and without intra-dialytic BP changes were compared using a two-sample t-test. To ascertain the relationship between IDH and clinical laboratory tests, we conducted a logistic regression analysis, accounting for age as a covariate. Statistical analyses were performed using SPSS Statistics ver. 25.0 and SAS® Analytics Pro Version 9.4.

RESULTS

1. Characteristics of the patients

We included 28 hemodialysis patients who consented to undergo ABPM, of which 11 were males and 17 were females. The average age of the participants was 57.4 years. Out of these, 16 patients (57.1%) had diabetes, 5 (17.9%) had angiography-confirmed coronary artery disease, and 1 (3.6%) had cerebrovascular disease (Table 1). Every patient was on at least two types of anti-hypertensive medications, which included calcium channel blockers, beta-blockers, and angiotensin receptor blockers.

2. Changes in BP during and after hemodialysis

Ambulatory monitoring showed that patients had elevated BP compared to their resting BP during hemodialysis (Fig. 2). During hemodialysis treatment, the mean SBP was 142.26 (107.20-186.80) mmHg and the mean DBP was 74.59

Table 1. Characteristics of the patients

	N=28 (%)	Range
Age	57.54±11.52	31.00-74.00
Male	11 (39.3)	
Diabetes	16 (27.1)	
Ischemic heart disease	5 (17.9)	
CVA	1 (3.6)	
BUN (mg/dL)	59±12	34.01-78.63
Creatinine (mg/dL)	10.45±2.80	4.39-17.95
Albumin (g/dL)	4.0±0.3	3.44-4.45
iPTH (pg/mL)	319±193	8.10-742.20
URR (%)	72.80±7.62	55.30-84.14
LVMI (g/m^2)	107.60±21.01	77.00-147.30
LV EF (%)	63.33±9.10	36.90-75.80
Anti-HT Pill burden*/d	3.25±3.11	0.5-10.0

CVA, cerebrovascular accident; iPTH, intact parathyroid hormone; URR, urea reduction ratio; LVMI, left ventricular mass index; LV EF, left ventricular ejection fraction; HT, hypertensives. *Fixed dose combination was counted as 2 pills

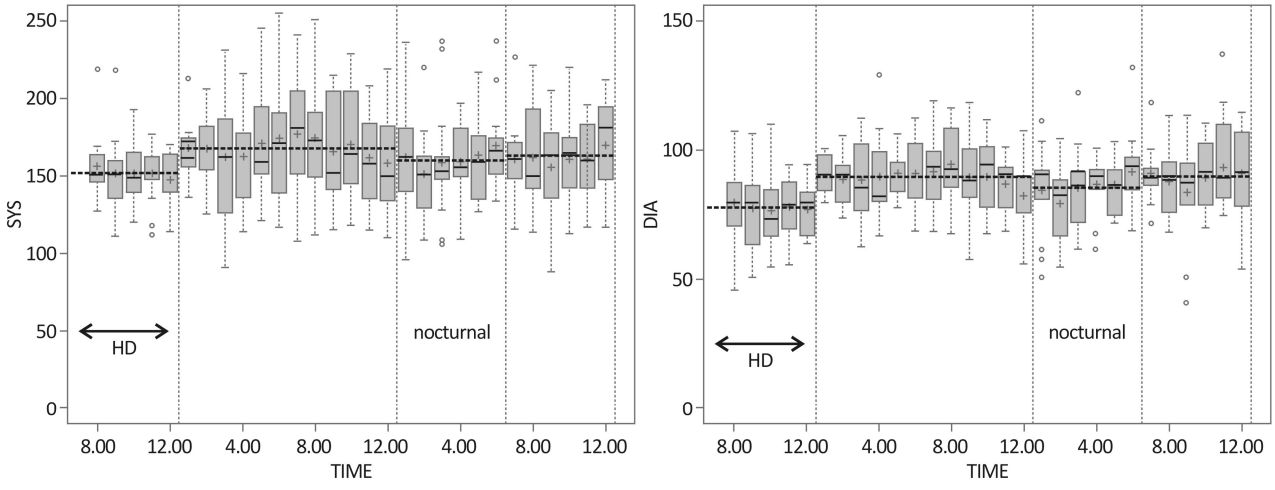

Fig. 2. Changes of BP during and after hemodialysis. The patients' systolic (left) and diastolic (right) BP were monitored by ABPM. Ambulatory BP was significantly higher than the BP recorded during the hemodialysis sessions.

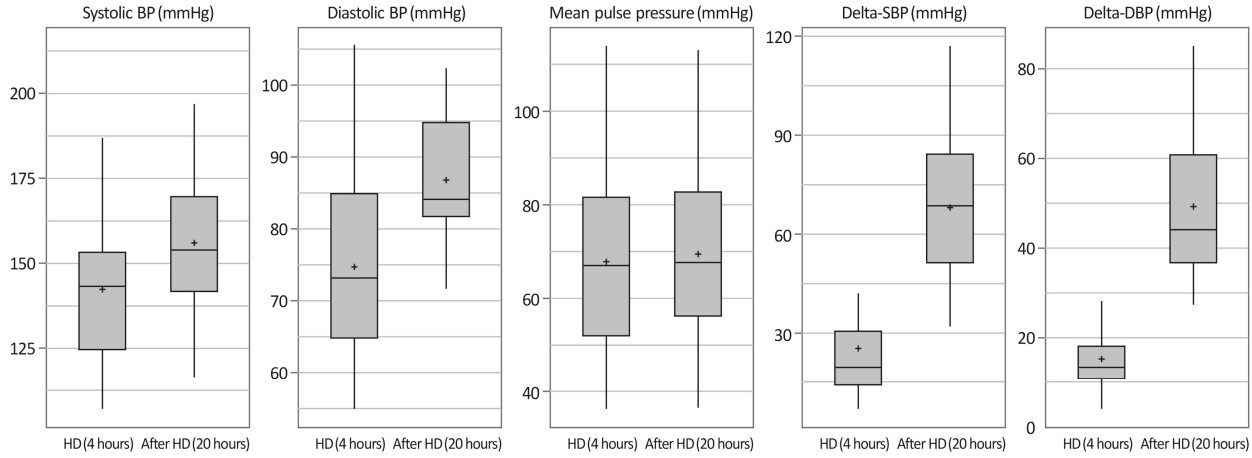

Fig. 3. Boxplot of BP differences during and after hemodialysis: Ambulatory BP monitoring indicated higher SBP, DBP, and greater BP differences post-dialysis.

Table 2. BP difference during and after hemodialysis session

	HD (4 hours)		After HD (20 hours)		p-value
	Mean	Range	Mean	Range	
Systolic BP (mmHg)	142.26	(107.20-186.80)	156.05	(116.17-213.92)	0.0003
Diastolic BP (mmHg)	74.59	(54.80-105.40)	86.82	(71.32-102.38)	<0.0001
Mean PP (mmHg)	67.66	(36.40-113.80)	69.23	(36.36-113.08)	0.5250
Delta-SBP (mmHg)	24.96	(7.00-103.00)	68.07	(32.00-117.00)	<0.0001
Delta-DBP (mmHg)	15.14	(4.00-42.00)	49.21	(27.00-85.00)	<0.0001

PP, pulse pressure; Delta-SBP/DBP, the average difference of SBP and DBP

(54.80-105.40) mmHg. Post-dialysis ambulatory measurements via ABPM revealed mean SBP and DBP values of 156.05 (116.14-213.92) mmHg and 86.32 (71.32-102.38) mmHg, respectively. These post-dialysis measurements demonstrated statistically significant differences when compared to the intra-dialysis mean SBP and DBP ($p=0.0003$ and $p<0.0001$, respectively) (Table 2). Moreover, the difference between SBP and DBP (delta-SBP and delta-DBP) during and after dialysis was also markedly increased after dialysis with statistical significance ($p<0.0001$) (Fig. 3). While the pulse pressure (PP) also showed an increase after dialysis, this change was not statistically significant (67.66±19.13 mmHg vs. 69.23±20.27 mmHg, respectively, $p=0.5250$).

3. Nocturnal BP changes in dialysis patients

We examined the nocturnal BP of dialysis patients in comparison to their daytime BP. The average daytime SBP and DBP were 153.88±22.55 mmHg and 84.12±10.37 mmHg respectively. In contrast, nocturnal SBP and DBP were 152.07 ±25.98 mmHg and 85.11±10.60 mmHg. Notably, we observed no significant nocturnal BP dipping during sleeping hours, with readings of 153.88/84.12 mmHg during the day compared to 152.07/85.11 mmHg at night (Fig. 2). Patients with diabetes showed higher SBP and pulse pressure during the night, though the difference was not statistically significant (155.98/83.77 mmHg versus 146.85/86.90 mmHg, $p=0.367$ for SBP, 0.449 for DBP).

4. Intradialytic hypotension and cardiovascular risk factors

We differentiated between two patient groups based on their SBP changes during dialysis: those with changes greater than 20 mmHg and those with changes less than 20 mmHg. Out of the 28 patients, 13 (46.4%) experienced IDH. The IDH group exhibited a more pronounced delta-SBP (148.48 vs. 136.87 mmHg, $p=0.0033$) and PP (76.02 vs. 60.43 mmHg,

Table 3. Difference between IDH group and non-IDH group

	IDH		Non-IDH		p-value
	Mean	Range	Mean	Range	
Age	62.54	(46.00-74.00)	53.13	(31.00-69.00)	0.0274
Systolic BP (mmHg)	148.48	(109.60-186.80)	136.87	(107.20-172.00)	0.1405
Diastolic BP (mmHg)	72.46	(54.80-99.00)	76.44	(55.40-105.40)	0.4272
Delta-SBP (mmHg)	36.38	(20.00-103.00)	15.07	(7.00-26.00)	0.0033
Delta-DBP (mmHg)	15.85	(6.00-30.00)	14.53	(4.00-42.00)	0.6752
Pulse pressure (mmHg)	76.02	(46.20-113.80)	60.43	(36.40-93.80)	0.0286
Nocturnal Systolic BP (mmHg)	156.15	(121.00-203.14)	148.53	(104.57-221.14)	0.4416
Nocturnal Diastolic BP (mmHg)	82.88	(66.57-101.00)	87.05	(67.86-109.14)	0.3027
LVMI (g/m^2)	106.44	(85.00-147.30)	108.60	(77.00-141.00)	0.7917
LV EF (%)	63.33	(36.90-75.80)	63.32	(44.50-75.60)	0.9976
Hemoglobin (g/dL)	10.33	(9.80-11.92)	10.48	(9.04-13.19)	0.6428
Pre-BUN (mg/dL)	53.03	(34.01-70.99)	64.14	(43.07-78.63)	0.0145
Post-BUN (mg/dL)	12.75	(7.93-23.91)	18.77	(11.29-27.13)	0.0015
Cholesterol (mg/dL)	136.00	(102.92-187.61)	134.39	(93.67-179.17)	0.8523
Albumin (g/dL)	3.87	(3.44-4.18)	4.14	(3.70-4.45)	0.0041

IDH, Intradialytic hypotension; LVMI, Left Ventricular Mass Index

Table 4. Logistic regression analysis to evaluate risk factors for IDH adjusted by age

	Estimate	Standard Error	Ward	p-value	Odds Ratio	95% CI
Delta-SBP (mmHg)	0.4554	0.1904	5.7207	0.0168	1.5768	1.0857-2.2902
Delta-DBP (mmHg)	0.0346	0.0507	0.4670	0.4944	1.0352	0.9374-1.1433
Pulse pressure (mmHg)	0.0446	0.0285	2.4477	0.1177	1.0457	0.9888-1.1058
LVMI (g/m^2)	0.0058	0.0213	0.0732	0.7867	1.0058	0.9647-1.0485
LV EF (%)	-0.0088	0.0451	0.0382	0.8449	0.9912	0.9073-1.0829
Hemoglobin (g/dL)	-0.1165	0.5375	0.0469	0.8285	0.8901	0.3104-2.5526
Pre-BUN (mg/dL)	-0.0745	0.0465	2.5682	0.1090	0.9282	0.8474-1.0168
Post-BUN (mg/dL)	-0.2738	0.1215	5.0802	0.0242	0.7605	0.5994-0.9649
Cholesterol (mg/dL)	0.0146	0.0200	0.5305	0.4664	1.0147	0.9757-1.0553
Albumin (g/dL)	-4.3480	2.3350	3.4680	0.0630	0.0130	0.0000-1.2560

Table 5. Comparison of post-dialysis blood pressure between IDH group and non-IDH group

	IDH (n=7)		Non-IDH (n=6)		p-value
	Mean	Range	Mean	Range	
Systolic BP MD to MN (mmHg)	164.18	(135.64-198.64)	169.52	(117.20-222.38)	0.7677
Diastolic BP MD to MN (mmHg)	86.58	(75.62-98.69)	92.78	(76.10-101.23)	0.2487

Only 13 patients on morning-session dialysis could be compared. MD, midday (noon); MN, midnight

p=0.0286) during hemodialysis compared to their counterparts. Furthermore, the IDH group had lower pre-dialysis BUN (53.03 vs. 64.14 mg/dL, p=0.0145), post-dialysis BUN (12.75 vs. 18.77 mg/dL, p=0.0015), and serum albumin levels (3.87 vs. 4.14 g/dL, p<0.005) (Table 3).

To evaluate the risk factors associated with IDH, we performed a logistic regression analysis, adjusting for age as a covariate due to its independent correlation with hypotension and cardiovascular risk factors. Notably, the important risk factors of IDH were delta-SBP during dialysis (OR=1.5768, 95% CI: 1.0857-2.2902, p=0.0168) and post-dialysis BUN (OR=0.7605, 95% CI: 0.5994-0.9649, p=0.0242).

Nonetheless, we found no clinical significance linking IDH with delta-DBP, PP, LV mass index, cholesterol, or albumin levels (Table 4).

To assess if there was a disparity in post-dialysis BP between the IDH and non-IDH groups, we examined the BP of morning dialysis patients from noon to midnight post-dialysis. However, there was no significant statistical difference between the two groups (Table 5).

DISCUSSION

This study provides pivotal data regarding real-world post-dialysis BP in Korean hemodialysis patients. Despite the acknowledged significance of BP regulation during dialysis, managing BP in ESKD patients remains challenging, particularly as many exhibit resistant hypertension. Medical practitioners often express concerns that strategies aimed at maintaining appropriate BP during dialysis might elevate the risk of IDH. Indeed, IDH emerges frequently as a hemodialysis complication, attributable to the external circulation and fluid removal fundamental to the dialysis process[5,9]. Studies indicate that approximately 20-30% of hemodialysis patients experience IDH, a condition closely associated with cardiovascular mortality[10], and potential triggers for myocardial ischemia and cerebrovascular insufficiency[10,11]. Nevertheless, Takeda et al. posited that even elevated pre-dialysis BP might not avert IDH[12], suggesting that there's no requisite for an augmented pre-dialysis BP to avoid IDH. Intriguingly, in our research, while the mean BP during hemodialysis aligned with the recommended BP guideline of 140/90 mmHg for hemodialysis, post-dialysis BP in clinical practice was markedly higher than anticipated. Our findings underscore the need for more rigorous BP management in dialysis clinics to mitigate cardiovascular morbidity.

Compared to the general population, hemodialysis patients typically exhibit higher rates of hypertension and a more frequent occurrence of mild to moderate LV hypertrophy[13], and a greater incidence of ischemic heart disease, all of which contribute to increased cardiovascular morbidity and mortality[13] Beyond these, hemodialysis patients have many other co-morbidities than the general population[14,15]. While Miskulin et al. observed no changes in LV mass despite intensive BP regulation[16], numerous studies have underscored the detrimental consequences of prolonged hypertension, linking it to both cardiovascular and cerebrovascular fatalities. Furthermore, IDH has been shown to not only elevate the rate of cardiovascular hospital admissions but also adversely impact the cognitive abilities of dialysis patients[11].

Dialysis patients often have elevated nocturnal BP, and it's common for them to lack the usual physiological drop in BP during sleep[17]. Nocturnal hypertension is closely associated with mortality. Wang et al. reported that nocturnal hypertension significantly increases the risk of kidney failure and cardiovascular mortality in patients with chronic kidney disease[18]. In ESKD patients, both hypertension and sympathetic tones are elevated. Due to increased vascular resistance, these patients often exhibit markedly higher nocturnal hypertension. Additionally, a higher incidence of depression in these patients can lead to sleep disturbances, further contributing to nocturnal hypertension[19]. Li et al. found that nocturnal BP is associated with pulse wave velocity in dialysis patients[20]. In our study, there was no statistically significant difference in daytime and nighttime BP between the IDH and non-IDH groups.

This study's strength lies in its presentation of BP readings for hemodialysis patients' post-dialysis sessions and its documentation of the prevalence of nocturnal hypertension in Korean ESKD patients. Surprisingly, the real-world post-dialysis BP was higher than anticipated, even when regulated during the dialysis session. Additionally, these patients did not exhibit a BP drop during sleep. While it remains uncertain if rigorous BP management during dialysis can enhance nocturnal BP regulation, the resting BP in dialysis clinics should be adjusted to be below the current BP guideline. Yet, concerns about IDH might persist as a challenge when enforcing intensive BP control. In our research, IDH correlated with lower BUN levels both before and after dialysis. A significant finding was the reduced serum albumin concentrations, known to be intricately linked to malnutrition[21]. Thus, there's an imperative to concentrate on elevating the nutritional status of patients to prevent IDH.

There are several limitations to this study. Firstly, we couldn't definitively determine the relationship between IDH, nocturnal BP, and cardiovascular complications, including LVH, morbidity, and ischemic heart disease, in the patients.

This uncertainty may arise because only a limited number of patients consented to undergo ABPM post-dialysis. Many patients on dialysis fear arm pain, dislike frequent BP measurements[22], and technically cannot continue ABPM the day following hemodialysis. Future studies with larger numbers of patients could reveal further precise data on ABPM. Secondly, based on our review of patients' sleep during the ABPM analysis, most patients complained of sleeping disturbance during nocturnal BP measurements. Although the general population also feels a disturbance in nocturnal BP monitoring, as large numbers of dialysis patients have sleeping disturbances, nocturnal BP of ESKD might be higher than expected. Buren et al. observed that an elevated intra-dialytic BP correlated with increased post-dialysis BP using a 44-hour ABPM[23]. If we had designed two days of ABPM which were technically difficult and hard to get informed consent, we would have found the difference between HD day and the next day and could have discovered more reliable sleeping BP. Thirdly, we found that the IDH group had higher delta-SBP, and controlling dialysis SBP is important for decreasing intra-dialytic BP changes. However, as delta-SBP itself includes intra-dialytic hypotension, delta-SBP might be a correlation, not a risk of IDH. Lastly, we couldn't compare the differences and effects among the classes of anti-hypertensive medication and BP changes based on their action time. Patients on dialysis often require higher doses of anti-hypertensives, complicating the task of solving the details of hypertension treatment. Future comprehensive, controlled trials might better elucidate the variances in dialysis BP resulting from different medications.

CONCLUSIONS

In conclusion, our research revealed significant elevations in post-dialysis BP among Korean hemodialysis patients, despite adhering to existing clinical guidelines during dialysis sessions. Additionally, the lack of a nocturnal BP dip indicates heightened cardiovascular risks for these individuals. This emphasizes the importance of more rigorous BP management after HD, while also considering the complexities of IDH.

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Disclosure

The authors have no potential conflicts of interest to disclosure.

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