

## Research article

# Pharmacist counseling is an important factor in lowering blood pressure of hemodialysis patients with hypertension

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## ABSTRACT

Hypertension is major comorbidity yet difficult to manage in hemodialysis patients. Pharmacist's role to improve the clinical outcome of hypertensive hemodialysis patients needs to be evaluated. The study objective was to evaluate the effect of pharmacist counseling in lowering systolic and diastolic blood pressure in hypertensive hemodialysis patients in hemodialysis unit of Fatmawati Hospital Jakarta in 2018, by controlling some confounders. The study used a quasi-experimental design with pretest-posttest, conducting on age, gender, education, smoking habit, and payment method-matched intervention and control groups. The research sample was taken by consecutive sampling method for 30 patients in the intervention group and 28 patients in the control group. Pharmacist counseling was carried out only in the intervention group. The parameter used were predialysis, intradialysis, and postdialysis systolic and diastolic blood pressure. The results showed that there were significant differences in pretest and posttest ( $p < 0.05$ ) for predialysis systolic and diastolic blood pressure in the counseling group. In multivariate analysis with backward method, pharmacist counseling was found to be the most determinant factor in reducing predialysis systolic blood pressure ( $p < 0.05$ ) controlled by education level. It also significantly reduced predialysis diastolic blood pressure controlled by gender, intradialysis systolic blood pressure, and intradialysis diastolic blood pressure controlled by age. In conclusion, pharmacist counseling was the most determinant factor in lowering pre- and intradialysis blood pressure in the hypertensive hemodialysis patient.

## 1. INTRODUCTION

There were at least 52,835 hemodialysis patients in Indonesia by the end of 2016. Fifty-one percents of patients were having hypertension as their comorbidity and 41% patients death were caused by cardiovascular diseases<sup>1</sup>. Studies report that treatment lowering blood pressure in hemodialysis patients is associated with decreased cardiovascular events, all-cause mortality, and mortality caused by cardiovascular diseases<sup>2,3</sup>.

Hypertension in chronic kidney disease and dialysis patients involves a multifactorial pathophysiology<sup>4</sup>. Pharmacology therapy to control blood pressure in hemodialysis patients is susceptible to expose patients to more medications and need to be individualized<sup>5</sup>

Being exposed to a bunch of medication, as in hemodialysis patients, can cause many problems such as medication error and patient nonadherence<sup>6</sup>. Those problems are the major factors of being not achieved patient's therapy target as uncontrolled and untreated hypertension in hemodialysis patients become a common issue. Continuous monitoring and pharmacist counseling will support the plan of care for those kinds of patients as those services can prevent medication errors and improve patient's adherence as well as discover patient's problems related to medications<sup>7</sup>

Even though some studies indicate ambulatory and home blood pressure monitoring have superior benefits as guidance for hypertension diagnosis, prognosis, and management in hemodialysis patients<sup>8,9</sup>, yet it can't be applicated in Indonesia whose majority of the patients neither having personal blood pressure monitor nor understanding how to use it. A study has shown that mean of pre-intra-post dialysis systolic blood pressure is not significantly different from that routine measured at home<sup>10</sup>. Other than that, hemodialysis unit blood pressure measurement is the routine procedure during hemodialysis session. Kidney Disease Outcome Quality Initiative (K/DOQI) recommends blood pressure target based on hemodialysis unit blood pressure measurement; predialysis should be < 140/90 mmHg and postdialysis < 130/80 mmHg<sup>11</sup>. Consequently, in absence of ambulatory and routine home blood pressure measurement, blood pressure measurement in health facilities as in hemodialysis unit, is needed as one of attempts in blood pressure monitoring.

There are several factors that influence the achievement of blood pressure control in hemodialysis patients, those factors are related to the pathophysiology of hypertension in hemodialysis patients as well as other factors that influence patient adherence to appropriately prescribed medications. Those factors considered as confounders are including

gender, age, level of education, smoking habits, duration of hemodialysis, frequency of hemodialysis, comorbidities, and interdialytic weight gain,<sup>6,12-19</sup>. Study that asses not only self-reported medication adherence, but also patient's clinical response as parameter to evaluate the effectiveness of pharmacy counseling and by taking into account those factors, has never been conducted in the hypertensive hemodialysis patients in Indonesia. Therefore, we aimed to evaluate the effect of pharmacists counseling in improving patient adherence so as lowering measurement of systolic and diastolic in pre-, intra-, and postdialysis, by controlling the confounders.

The objective of this study was to evaluate the effect of pharmacist counseling in lowering blood pressure of hemodialysis patient with hypertension guided by hemodialysis unit blood pressure monitoring in Fatmawati Hospital, Jakarta.

## 2. MATERIALS AND METHODS

### 2.1. Design

This was a quasi-experimental study with pretest–posttest controlled design. This study was conducted in a public hospital in Hospital Fatmawati Jakarta and carried out over six months, from April until September 2018.

### 2.2. Patients

Patients attending hemodialysis sessions in hemodialysis unit of Fatmawati Hospital in April 2018 were screened to participate in this study. Patients participated in this study were those who fulfilled all these following criteria: 19 years or older, receiving maintenance hemodialysis in hemodialysis unit of Fatmawati Hospital, were hypertensive or were taking antihypertensive agents, and consented to participate in the study. Patients who had any of the following criteria couldn't participate the study: pregnant women, patients who experienced hypotensive, patients taking any antihypertensive agent during dialysis, patients who had cognitive impairment, patients who were absent for two or more dialysis schedule in a month of study, and patients with incomplete data in medication record needed for the study.

$$\text{Minimum samples were calculated using } n = \frac{2\sigma^2(Z_{1-\alpha} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

With confidence interval 95% ( $Z_{1-\alpha} = 1.64$ ) and power of 80% ( $Z_{1-\beta} = 0.84$ ), minimum number of patients required for each group was 27 patients. To anticipate patients dropping out (dying, not undergoing hemodialysis more than twice, receiving more potent antihypertensive regimen, or resigning from study), a target sample size of 60 patients (30 patient for the intervention group and 30 for the control group) was selected. For ethical reasons and to minimize communication between groups, patients who met the sample criteria were assigned consecutively to the control group or the intervention group based on their different hemodialysis schedule. Counseling was carried out only in the intervention group by pharmacists for 15-20 minutes per patient. Each patient received 4 sessions of counseling at a 1-week interval.

### 2.3. Counseling Materials

The counseling materials were related to drug therapy and salt restriction in managing the patients blood pressure. Counseling materials were divided into several topics. Each counseling session has different counseling topics and targets. The first session was to explore or recall patients' understanding of diseases, drugs, and problems that prevent patients from taking their medicine. The second session was to educate patients about how antihypertensive drugs work, how to take and store drugs correctly, how to adhere to salt and fluid restriction in their diets, and the benefits they will feel if they adhere to their therapy properly. The third session was to listen to their complaints about the disease and the treatment they received. This was an opportunity to explore about their complications or comorbidities that might not been resolved as well as to motivate them to adhere to medication and blood pressure control. The fourth session was a reminder of what had been given in several counseling sessions, re-checking patients' understanding of treatment and guiding back to medication adherence. At each session, checks were also made on how they take their medicine and medication adherence. If drug-related problem was found, appropriate follow-up was given, in coordination with the relevant health personnel.

### 2.4. Outcomes

Parameters used were their pre-, intra-,

and postdialysis blood pressure. Predialysis blood pressure was measured before dialysis started. Intradialysis blood pressure was the average of three times blood pressure readings during dialysis. Postdialysis blood pressure was measured after dialysis finished. All those blood pressure measurements were measured by automatic blood pressure monitor that was integrated with hemodialysis machine and recorded by blinded to patient's group staff nurses. The effect of counseling on each blood pressure parameter was assessed by the proportion of patients whose their pre-, intra-, and postdialysis blood pressure declined in the end of the study and by its relative risk compared to the control group. This study also analyzed the pretest to posttest blood pressure changes. Interdialytic weight gain (IDWG), defined as current postdialysis – previous postdialysis bodyweight, was used to evaluate patients adherence to fluid and salt restriction. IDWG was assessed as volume accumulation played an important contributor of hypertension in hemodialysis patients. To evaluate patients adherence to antihypertensive medications, the medication adherence questionnaire (MAQ) based on 4-item Morisky scale were used<sup>20</sup>. Patient responses to MAQ were scored (1 – 4) and then classified to low, medium, and high level of adherence.

### 2.5. Statistics

Statistical Package for the Social Sciences (SPSS) software, version 20 was used to manage and process data analysis. Chi-square test was used to detect differences between categorical variables. For continuous data, the independent-t test was used to compare mean between groups if data distributed normally, otherwise, Mann-Whitney test was used. Paired t-test was used to compare means at pretest and posttest if data distributed normally, otherwise, Wilcoxon-Sign was used. The multivariate analysis was done by multivariable logistic regression, due to dichotomous categoric of dependent variables. The multivariable logistic regression analysis was using the Backward Likelihood Ratio (LR) method. This method makes it possible to include all independent variables that were thought to have a significant effect in the bivariate analysis ( $p < 0.25$ ), then eliminate those variables one by one until the most meaningful

variables remain. The significance level was set at  $p < 0.05$  and confidence interval (CI) of 95 %.

### 3. RESULTS

Among 189 screened patients, only 65 patients met inclusion criteria. Since there were dropouts during follow up, only 58 patients ended up being completed the study, as follow: 30 patients in the intervention group and 28 patients in the control group. Seven patients were dropped out as three in the intervention group was hospitalized and absent for counseling schedule and posttest, while four in the control group was hospitalized and absence for posttest.

Demographics characteristics were homogenous for both study groups as shown in Table 1. Clinical characteristics and the types of antihy-

pertensive agents that were used by the patients are shown in Table 2. Significant differences were found between study groups in terms of the number and type of antihypertensive agent.

The differences of systolic and diastolic blood pressure between baseline (pretest) and after series of pharmacist counseling (posttest) are shown in Table 3. In the intervention group, there were significant reduction in mean systolic and diastolic blood pressure at predialysis measurement, but no difference was found at intradialysis as well as postdialysis measurement. Systolic blood pressure at predialysis declined by 10.2 mmHg in the intervention group ( $p = 0.015$ ), meanwhile it increased in the control group ( $p = 0.015$ ). Diastolic blood pressure at predialysis declined by 6.06 mmHg in the intervention group ( $p = 0.019$ ), yet it slightly increased in the control group ( $p = 0.08$ ).

**Table 1.** Demographic characteristic of the two groups

Characteristic	Intervention (%) <sup>a</sup>	Control (%) <sup>a</sup>	Total (%) <sup>b</sup>	<i>p</i> -value <sup>*</sup>
Gender				0.100
Male	14 (47.7%)	20 (71.4%)	34 (58.6%)	
Female	16 (53.3%)	8 (28.6%)	24 (41.4%)	
Age				0.578
19 – 49 years old	15 (50.0%)	11 (39.3%)	26 (44.8%)	
50 years old - more	15 (50.0%)	17 (60.7%)	32 (55.2%)	
Mean $\pm$ SD	48.70 $\pm$ 15.20	54.64 $\pm$ 12.86		0.115
Education Level				0.587
Basic ( $\leq$ 9 years of education)	7 (23.3%)	4 (14.3%)	11 (19.0%)	
Advanced ( $>$ 9 years of education)	23 (76.7%)	24 (85.7%)	47 (81.0%)	
Smoking habit				0.483
Never	30 (100%)	27 (96.4%)	57 (98.3%)	
Active smoker	-	1 (3.6%)	1 (3.6%)	
Payment				
Insurance	30 (100%)	28 (100%)	58 (100.0%)	

<sup>\*</sup> *p*-value was obtained using Chi-square test for categorical data and independent t-test for continuous data, statistically significant difference if  $< 0.05$ ;

<sup>a</sup> Percent within study group, intervention group:  $n = 30$ , control group:  $n = 28$

<sup>b</sup> Percent within total,  $n = 58$

**Table 2.** Clinical characteristic of the two study groups

Characteristic	Intervention (%) <sup>a</sup>	Control (%) <sup>a</sup>	Total (%) <sup>b</sup>	p-value*
Hemodialysis duration				1.000
≤6 months	4 (13.3%)	4 (14.3%)	8 (13.8%)	
>6 months	26 (86.7%)	24 (85.7%)	50 (86.2%)	
Hemodialysis frequency				1.000
2 session/week	27 (90%)	26 (92.9%)	53 (91.4%)	
3 session/week	3 (10%)	2 (7.1%)	5 (8.6%)	
Comorbidity				1.000
Absent	12 (40%)	12 (42.9%)	24 (41.4%)	
Present	18 (60%)	16 (57.1%)	34 (58.6%)	
Number of antihypertensive agents				
≤ 2 agents	17 (56.7%)	24 (85.7%)	41 (70.7%)	0.032*
≥ 3 agents	13 (43.3%)	4 (14.3%)	17 (29.3%)	
Type of antihypertensive agents				
Centrally acting agent	19 (63.3%)	7 (25.0%)	26 (44.8%)	0.008*
DHP CCB	24 (80%)	19 (67.9%)	43 (74.1%)	0.450
NDHP CCB	1 (3.3%)	-	1 (1.7%)	1.000
ARB	17 (56.7%)	8 (28.6%)	25 (43.1%)	0.058
ACEI	3 (10.0%)	2 (7.1%)	5 (8.6%)	1.000
Beta blocker	1 (3.3%)	2 (7.1%)	3 (5.2%)	0.605
Mix alpha/beta antagonist	1 (3.3%)	-	1 (1.7%)	1.000
Blood pressure (mmHg)				
Systolic predialysis	167.67±20.23	158.75±5.42		0.118d
Diastolic predialysis	91.93±14.15	85.00±17.89		0.099c
Systolic intradialysis	164.65±17.79	158.08±4.29		0.629d
Diastolic intradialysis	87.87±11.36	84.58±14.73		0.343c
Systolic postdialysis	160.80±22.89	150.21±24.16		0.092c
Diastolic postdialysis	87.97±2.67	81.96±13.67		0.129d
MAQ Pretest				0.561
Low	10 (33.3%)	13 (46.4%)		
Medium	18 (60.0%)	14 (50.0%)		
High	2 (6.7%)	1 (3.6%)		
MAQ Posttest				0.029*
Low	1 (3.3%)	8 (28.6%)		
Medium	21 (70.0%)	14 (50.0%)		
High	8 (26.7%)	6 (21.4%)		

DHP CCB, dihydropyridine calcium channel blocker; NDHP CCB, Nondihydropyridine calcium channel blocker; ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor; MAQ, medication adherence questionnaire

\* *p*-value was obtained using Chi-square test for categorical data and <sup>c</sup> independent t-test or <sup>d</sup> Mann Whitney test for continuous data, statistically significant difference if *p* < 0.05

<sup>a</sup> Percent within study group, intervention group: *n* = 30, control group: *n* = 28

<sup>b</sup> Percent within total, *n* = 58



**Table 3.** Comparison of change in mean dialysis blood pressure from pretest to posttest between two study groups

Parameter	Groups <sup>a</sup>	Pretest Mean $\pm$ SEM	Posttest Mean $\pm$ SEM	Changes	p-value*
Systolic	Intervention	167.67 $\pm$ 20.23	157.47 $\pm$ 20.20	-10.2 $\pm$ 3.94	0.015 <sup>c</sup>
Predialysis	Control	158.75 $\pm$ 5.42	166.96 $\pm$ 26.95	8.21 $\pm$ 5.88	0.015 <sup>f</sup>
Diastolic	Intervention	91.93 $\pm$ 14.15	85.86 $\pm$ 14.83	-6.06 $\pm$ 2.43	0.019 <sup>c</sup>
Predialysis	Control	85.00 $\pm$ 17.29	91.21 $\pm$ 18.07	6.21 $\pm$ 3.42	0.080 <sup>f</sup>
Systolic	Intervention	164.65 $\pm$ 17.79	158.34 $\pm$ 16.34	-6.31 $\pm$ 3.45	0.078 <sup>c</sup>
Intradialysis	Control	158.08 $\pm$ 4.29	168.52 $\pm$ 26.50	10.44 $\pm$ 4.21	0.021 <sup>f</sup>
Diastolic	Intervention	87.87 $\pm$ 11.36	84.57 $\pm$ 2.17	-3.30 $\pm$ 2.23	0.150 <sup>f</sup>
Intradialysis	Control	84.58 $\pm$ 14.73	89.82 $\pm$ 16.93	5.24 $\pm$ 2.35	0.035 <sup>c</sup>
Systolic	Intervention	160.80 $\pm$ 22.89	154.93 $\pm$ 22.74	-5.86 $\pm$ 5.33	0.280 <sup>c</sup>
Postdialysis	Control	150.21 $\pm$ 24.16	165.82 $\pm$ 5.21	15.61 $\pm$ 4.79	0.001 <sup>f</sup>
Diastolic	Intervention	87.97 $\pm$ 2.68	81.37 $\pm$ 2.07	-6.60 $\pm$ 3.48	0.071 <sup>f</sup>
Postdialysis	Control	81.96 $\pm$ 13.67	86.43 $\pm$ 12.26	4.46 $\pm$ 2.50	0.086 <sup>c</sup>
IDWG	Intervention	2.03 $\pm$ 0.21	1.64 $\pm$ 0.25	-0.39 $\pm$ 0.25	0.134 <sup>f</sup>
	Control	1.86 $\pm$ 0.20	1.65 $\pm$ 0.23	-0.22 $\pm$ 0.20	0.306 <sup>c</sup>

IDWG, interdialytic weight gain

\* p-value was obtained using: <sup>c</sup> paired t-test or <sup>f</sup> Wilcoxon Sign test, statistically significant difference if p<0.05<sup>a</sup> intervention group: n = 30, control group: n = 28

The effect of counseling in lowering systolic and diastolic blood pressure at pre-, intra-, and postdialysis measurement are shown in Table 4. In the intervention group, 18 out of 30 (60%) patients had predialysis systolic blood pressure declined, while in the control group, only 7 out of 28 (25%) patients had it decline ( $p = 0.015$ ). For predialysis diastolic blood pressure, 23 out of 30 (76.75%) patients in the intervention group had it decline, while 5 out of 28 (17.9%) in the control group had it decline ( $p < 0.001$ ). Similarly for systolic and diastolic blood pressure at intradialysis measurement, more patients in the intervention group were having their blood pressure declined compared to the control group ( $p = 0.036$  and  $p = 0.015$ , respectively). There was no difference in the proportion of patients whose postdialysis systolic

and diastolic blood pressure declined between groups.

The effect of counseling on each blood pressure parameter could be seen also from the value of relative risk (RR). The RR value of counseling in predialysis systolic blood pressure was 2.4 with 95% CI 1.186 – 4.857, so it was said that patients who received counseling were 2.4 times more likely to experience a decline in predialysis systolic blood pressure than patients without counseling. Based on the data in Table 4, patients who received counseling had a significant opportunity to experience a decline in predialysis diastolic pressure, intradialysis systolic, and intradialysis diastolic by 4.29, 1.87, and 2.4 times greater than patients who didn't get counseling session, respectively.

Based on the bivariate analysis using Chi-Square, treatment and confounding variables that suspected to be have a significant relationship or influence on the decrease in blood pressure ( $p < 0.25$ ), namely gender, age, education level, as shown in Table 5, were followed by logistic regression analysis multivariable using the Backward Likelihood Ratio (LR) method, as shown in Table 6. Based on the bivariate analysis, the frequency of hemodialysis had the opportunity as a covariate in multivariate analysis ( $p < 0.25$ ). However, because the proportion of patients with hemodialysis frequency 3 times a week was very small compared to patients with a frequency of 2 times a week and the proportion

between the two groups was similar, the frequency of hemodialysis was not included as a covariate in the multivariate analysis

Multivariate analysis by logistic regression showed that pharmacist counseling was the most determinant factor on reducing patient's blood pressure. The effect of pharmacist counseling: (a) significantly reduced predialysis systolic blood pressure controlled by education level; (b) significantly reduced predialysis diastolic blood pressure controlled by gender, and (c) significantly reduced intradialysis blood pressure, and (d) significantly reduced intradialysis diastolic blood pressure controlled by age.

**Table 4.** Difference in proportion of patients with declined blood pressure based on counseling treatment

	Blood pressure			<i>p</i> -value*	RR	95% CI	
	Declined	Not declined	Total			Lower	Upper
Predialysis Systolic							
Intervention	18 (60.0%)	12 (40.0%)	30 (100.0%)	0.015*	2.400	1.186	4.857
Control	7 (25.0%)	21 (75.0%)	28 (100.0%)				
Predialysis Diastolic							
Intervention	23 (76.7%)	7 (23.3%)	30 (100.0%)	0.000*	4.293	1.894	9.734
Control	5 (17.9%)	23 (82.1%)	28 (100.0%)				
Intradialysis Systolic							
Intervention	20 (66.7%)	10 (33.3%)	30 (100.0%)	0.036*	1.867	1.069	3.260
Control	10 (35.7%)	18 (64.3%)	28 (100.0%)				
Intradialysis Diastolic							
Intervention	18 (60%)	12 (40%)	30 (100.0%)	0.015*	2.400	1.186	4.857
Control	7 (25%)	21 (75%)	28 (100.0%)				
Postdialysis Systolic							
Intervention	14 (46.7%)	16 (53.3%)	30 (100.0%)	0.081	2.178	.973	4.875
Control	6 (21.4%)	22 (78.6%)	28 (100.0%)				
Postdialysis Diastolic							
Intervention	16 (53.3%)	14 (46.7%)	30 (100.0%)	0.100	1.867	.951	3.665
Control	8 (28.6%)	20 (71.4%)	28 (100.0%)				

RR, relative risk; CI, confidence interval

\* *p*-value was obtained using Chi-square test for categorical data, statistically significant difference if  $< 0.05$ ;

**Table 5.** Confounding variable influencing the declining of hemodialysis unit blood pressure measurement

Independent variables	Systolic predialysis		Diastolic predialysis		Systolik intradialysis		Diastolic intradialysis		Systolic postdialysis		Diastolic Postdialysis
	Not declined	Declined	Not declined	Declined	Not declined	Declined	Not declined	Declined	Not declined	Declined	Not declined
Gender											
Male	23 (67.6%)	11 (32.4%)	23 (67.6%)	11 (32.4%)	18 (52.9%)	16 (47.1%)	21 (61.8%)	13 (38.2%)	22 (64.7%)	12 (35.3%)	21 (61.8%)
Female	10 (41.7%)	14 (58.3%)	7 (29.2%)	17 (70.8%)	10 (41.7%)	14 (58.3%)	12 (50.0%)	12 (50.0%)	16 (66.7%)	8 (33.3%)	13 (54.2%)
<i>p</i> -value*	0.089		0.009*		0.562		0.534		1.000		0.758
Age											
19 –49 years old	15 (57.7%)	11 (42.3%)	14 (53.8%)	12 (46.2%)	13 (50.0%)	13 (50.0%)	18 (69.2%)	8 (30.8%)	19 (73.1%)	7 (26.9%)	15 (57.7%)
50 years old - more	18 (56.2%)	14 (43.8%)	16 (50.0%)	16 (50.0%)	15 (46.9%)	17 (53.1%)	15 (46.9%)	17 (53.1%)	19 (59.4%)	13 (40.6%)	19 (59.4%)
<i>p</i> -value	1.000		0.978		1.000		0.149		0.146		1.000
Education level											
Basic	3 (27.3%)	8 (72.7%)	4 (36.4%)	7 (63.6%)	3 (27.3%)	8 (72.2%)	5 (45.5%)	6 (54.5%)	8 (72.7%)	3 (27.3%)	5 (45.5%)
Advanced	30 (63.8%)	17 (36.2%)	26 (55.3%)	21 (44.7%)	25 (53.2%)	22 (46.8%)	28 (59.6%)	19 (40.4%)	30 (63.8%)	17 (36.2%)	29 (61.7%)
<i>p</i> -value	0.042*		0.425		0.225		0.504		0.731		0.498
Smoking habit											
Never	32 (56.1%)	25 (43.9%)	29 (50.9%)	28 (49.1%)	27 (47.4%)	30 (52.6%)	32 (56.1%)	25 (43.9%)	37 (64.9%)	20 (35.1%)	33 (57.9%)
Active smoker	1 (100%)	.	1 (100%)	.	1 (100%)	.	1 (100%)	.	1 (100%)	.	1 (100%)
<i>p</i> -value	1.000		1.000		0.483		1.000		1.000		1.000



**Table 5.** Confounding variable influencing the declining of hemodialysis unit blood pressure measurement (cont.)

Independent variables	Systolic predialysis		Diastolic predialysis		Systolik intradialysis		Diastolic intradialysis		Systolic postdialysis		Diastolic Postdialysis	
	Not declined	Declined	Not declined	Declined	Not declined	Declined	Not declined	Declined	Not declined	Declined	Not declined	Declined
Hemodialysis duration												
□ 6 months	4 (50%)	4 (50%)	3 (37.5%)	5 (62.5%)	4 (50%)	4 (50%)	3 (37.5%)	5 (62.5%)	4 (50%)	4 (50%)	6 (75.0%)	2 (25.0%)
>6 months	29 (58.0%)	21 (42.0%)	27 (54.0%)	23 (46.0%)	24 (48.0%)	26 (52.0%)	30 (60.0%)	20 (40.0%)	34 (68.0%)	16 (32.0%)	28 (56.0%)	22 (44.0%)
<i>p</i> -value	0.715		0.464		1.000		0.272		0.428		0.449	
Hemodialysis frequency												
2 session/week	28 (52.8%)	25 (47.2%)	25 (49.1%)	27 (50.9%)	24 (45.3%)	29 (54.7%)	31 (58.5%)	22 (41.5%)	34 (64.2%)	19 (35.8%)	31 (58.5%)	22 (41.5%)
3 session/week	5 (100%)	0 (0.0%)	4 (80.0%)	1 (20.0%)	4 (80.0%)	1 (20.0%)	2 (40.0%)	3 (60.0%)	4 (80.0%)	1 (20.0%)	3 (60.0%)	2 (40.0%)
<i>p</i> -value	0.063		0.354		0.187		0.643		0.650		1.000	
Comorbidities <sup>a</sup>												
Absent	13 (54.2%)	11 (45.8%)	13 (54.2%)	11 (45.8%)	12 (50.0%)	12 (50.0%)	13 (54.2%)	11 (45.8%)	17 (70.8%)	7 (29.2%)	14 (58.3%)	10 (41.7%)
Present	20 (58.8%)	14 (41.2%)	17 (50.0%)	17 (50.0%)	16 (47.1%)	18 (52.9%)	20 (58.8%)	14 (41.2%)	21 (61.8%)	13 (38.2%)	20 (58.8%)	14 (41.2%)
<i>p</i> -value	0.933		0.963		1.000		0.933		0.663		1.000	
Interdialytic Weight Gained												
Not declined	18 (62.1%)	11 (37.9%)	14 (48.3%)	15 (51.7%)	13 (44.8%)	16 (55.2%)	18 (62.1%)	11 (37.9%)	18 (62.1%)	11 (37.9%)	15 (51.7%)	14 (48.3%)
Declined	15 (51.7%)	14 (48.3%)	16 (55.2%)	13 (44.8%)	15 (51.7%)	14 (48.3%)	15 (51.7%)	14 (48.3%)	20 (69.0%)	9 (31.0%)	19 (65.5%)	10 (34.5%)
<i>p</i> -value	0.596		0.793		0.793		0.596		0.782		0.424	

\**p*-value was obtained using Chi-square test for categorical data, statically significant difference if < 0.05<sup>a</sup>Comorbidities, present if patient had any of this comorbidities: diabetes melitus, cardiac disease, and hypercholesterol

**Table 6.** Multivariate analysis on factors influencing blood pressure

Dependent	Independent variables	OR	95% CI		<i>p</i> -value*
			Lower	Upper	
Predialysis Systolic	Groups				0.011*
	Counseling	4.959	1.454	16.908	
	Without counseling	1	Reference		
	Education				0.065
	Basic education	5.260	0.902	30.686	
	Advanced education	1	Reference		
Predialysis Diastolic	Groups				0.000*
	Counseling	14.080	3.609	54.925	
	Without counseling	1	Reference		
	Gender				0.032*
	Female	4.517	1.139	17.915	
	Male	1	Reference		
Intradialysis Systolic	Groups				0.015*
	Counseling	4.031	1.309	12.414	
	Without counseling	1	Reference		
Intradialysis Diastolic	Groups				0.005*
	Counseling	6.043	1.741	20.975	
	Without counseling	1	Reference		
	Age				0.037*
	50 years old - more	3.776	1.085	13.141	
	19 – 49 years old	1	Reference		

\*statistically significant difference if *p*-value < 0.05

At baseline, no difference was found in patient medication adherence between groups. However, at the end of the study, there was a significant difference between groups in the proportion of patients self-report medication adherence, ( $p = 0.029$ ). At the end of study, patients reported high medication adherence by 26.7% (8/30) in the intervention group, compared to 21.4% (6/28) in the control group and medium medication adherence by 70% (21/30) in the intervention group, compared to 50% (14/28) in the control group (Table 1).

In addition to patient education and patient adherence in pharmacological treatment, patients were approached for counseling regarding and fluid/salt restriction. IDWG represent volume accumulation between dialysis and may be used as a parameter to evaluate patients adherence to fluid and salt restriction. No difference of IDWG ( $p = 0.134$ ) was found between pretest ( $2.03 \pm 1.15$  kg)

and posttest ( $1.64 \pm 0.25$  kg) in the intervention group. The difference of IDWG was neither be found between pretest and posttest in the control group. This result is shown in Table 3.

#### 4. DISCUSSION

The demographic characteristics of patients in this study showed that the majority of hemodialysis patients with hypertension were male and over 50 years old. The results are consistent with the data on population of hemodialysis and chronic renal failure patients in Indonesia<sup>21,1</sup>. Another study involving more participants from several countries ( $n = 206,374$  patients), showed that the majority of patients from all age groups undergoing dialysis were male (59%) and the average age in men was  $61.96 \pm 14.6$  and women was  $63.16 \pm 14.5$  years<sup>22</sup> treatment, and outcomes of individuals with end-stage renal disease undergoing dialysis might reveal treatment inequalities and targets to improve

sex-specific patient care. Here we describe hemodialysis prevalence and patient characteristics by sex, compare the adult male-to-female mortality rate with data from the general population, and evaluate sex interactions with mortality.

**METHODS AND FINDINGS:** We assessed the Human Mortality Database and 206,374 patients receiving hemodialysis from 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, the UK, and the US.

All participants were guaranteed by the national health insurance. Based on the ninth Indonesian Renal Registry (IRR) report in 2017, there was an increase in the number of active hemodialysis patients in 2016. This showed that more patients could undergo longer hemodialysis and national health insurance factors played a role in the continuation of this therapy<sup>1</sup>.

Except in urgency or emergency hypertension situations, hemodialysis patients must achieve dry weight before being given antihypertensive therapy. Achievement of dry weight can be done by limiting salt intake and fluids, as well as having adequate dialysis regimens<sup>11,23</sup>.

Several studies showed that reducing body dry weight gradually could effectively reduce blood pressure. The Dry-Weight Study Reduction in Hypertensive Hemodialysis Patients (DRIP) is the first randomized controlled study to show that a decrease in body dry weight will reduce ambulatory blood pressure in hemodialysis patients<sup>24</sup>. Randomized, controlled trials lack power to establish benefits of antihypertensive therapy. Patients on long-term dialysis participating in randomized, controlled trials and receiving antihypertensive drug therapy were the subject of this meta-analysis. Outcomes assessed were the hazard ratio of cardiovascular events and all-cause mortality in treated group compared with controls. Among 1202 patients who we identified in 5 studies, the overall benefit of antihypertensive therapy compared with the control or placebo group had a combined hazard ratio for cardiovascular events of 0.69 (95% CI: 0.56 to 0.84). When dry weight has been reached, blood pressure will normalize but it may take weeks to months<sup>25</sup>. A study comparing body weight and blood pressure showed the decrease in mean arterial pressure ( $111.3 \pm 2.5$  to  $94.4 \pm 1.7$  mm Hg) after reduction of patients body weight to targeted body

dry weight during first 6 month of hemodialysis onset and it remained stable after that<sup>26</sup>. The mortality rate is very high at the initiation phase, up to 6 months, because the patient has several uremic symptoms, including protein energy waste, infection, and cardiovascular disease<sup>27</sup>. In this study, majority of patients had undergone hemodialysis more than 6 month and it could be expected that blood pressure status was having minimal effect of initiation phase.

Patients with chronic kidney failure are often given several medications. The combination of antihypertensive agents with other medications will add polypharmacy in the treatment of hemodialysis patients. Increasing polypharmacy will increase the risk of nonadherence in hemodialysis patients. Simplifying treatment regimens can be an effort to improve patients adherence to medications.

The most widely used antihypertensive agents in both groups were dihydropyridine calcium channel blockers such as amlodipine and nifedipine. These drugs were mostly chosen because of their benefits to the cardiovascular and kidney systems. A randomized controlled study showed that amlodipine provides cardiovascular benefits such as myocardial infarction and ischemic stroke, compared to placebo<sup>28</sup>. A meta-analysis and systematic review has shown that this class has the same effect as angiotensin aldosterone renin blockers on cardiovascular and kidney protection but doesn't pose a risk of hyperkalemia as well as in angiotensin converting inhibitors or angiotensin receptor blockers<sup>29</sup>. The pharmacokinetics of calcium channel blockers do not change among patients undergoing dialysis and these drugs are generally not dialyzed so that they don't require dose adjustment<sup>5</sup>.

The mean systolic and diastolic blood pressure of the patients both at pre-, intra-, and postdialysis in the intervention group tended to be higher than the control group, but this difference was not significant. The mean predialysis as well as postdialysis blood pressure in both groups had not reached the target of controlled blood pressure for hemodialysis patients recommended by K/DOQI, which was < 140/90 mmHg for predialysis and < 130/80 mmHg for postdialysis<sup>11</sup>.

The role of the pharmacist in blood pressure management has been reported in many studies.

A literature review and meta-analysis showed that pharmacist intervention improved patient adherence to medication and their blood pressure control<sup>30</sup>. Pharmacists interventions itself range from providing information regarding patient medication to the more complex role involving medication monitoring, collaborating with other physicians, and counseling to support patient's understanding and their adherence to medication over a number of visits.

Blood pressure control in hemodialysis patients is therapeutic challenging as unique variability in blood pressure is experienced by dialysis patient and complexity of treatment is being involved. Therefore, every hypertensive patient on hemodialysis is in need for pharmacist intervention such as counseling and continuous monitoring as it can give benefit to prevent medication error and to improve the outcome.

The result of this present study showed that pharmacist counseling could have a positive impact on blood pressure control. The intervention group experienced a decrease in predialysis blood pressure at the time of posttest which was significantly different than at the pretest. Whereas in the control group, patients experienced a rise in blood pressure. These deterioration haven't found a plausible explanation. The proportion of patients whose blood pressure declined after received several counseling sessions were higher compared to that in the control group, significantly in terms of predialysis and intradialysis blood pressure, with some confounders namely sex, age, and education level as in Tables 5 and 6. The result was in line with studies that also showed positive outcome in home blood pressure control involving patient education or collaboration care of pharmacist and physician in the management of blood pressure in dialysis patients<sup>31</sup>.

The results of this study showed that more female patients (70.8%) gave significantly improvements to predialysis diastolic blood pressure than male patients (32.4%). The role of gender in blood pressure regulation has not been fully explained. Several other studies have shown that this mechanism is not easily understood and is likely to involve the influence of sex steroids or sex chromosomes<sup>32</sup>.

Age variables need to be a concern in managing a patients blood pressure. In this study, it could be seen that the age factor had an influence on the decrease of hypertensive hemodialysis patient

blood pressure. This could be because age was related to changes in physiology and regulation of blood pressure. Aging involves various physiological changes such as increased arterial stiffness, widening pulse pressure, changes in renin and aldosterone levels, decreased renal salt excretion, decreased kidney function, changes in sensitivity and function of the autonomic nervous system and function as well as changes in endothelial functions which may not only affect blood pressure but can also influence individual responses to pharmacotherapy used in order to manage hypertension and prevent end organ damage and other complications associated with poor blood pressure control<sup>33</sup>.

Education levels can affect patients understanding of treatment and compliance<sup>34,35</sup>. Increasing patient compliance will provide better patient clinical outcomes<sup>36</sup>. The results of systematic review study showed that patients with higher levels of education would have a positive effect on compliance<sup>35</sup>. The results of this study showed the contrary – patients with basic education level had significantly better blood pressure control improvement than patients with advanced education level. Some factors that might be further involved in compliance apart from education levels were patients awareness and willingness to follow the instructions or advice given during counseling session.

The population of hemodialysis patients at Fatmawati General Hospital mostly undergo hemodialysis twice a week and each hemodialysis session is 4 hours long. A study showed that the duration and / or frequency of hemodialysis per week associated with improvement in blood pressure management. Increased circulation volume has become a more important role in hemodialysis patients because of the limited ability of patients with end-stage renal failure to remove excess fluid. Longer duration and / or more frequent hemodialysis sessions per week can reduce adverse effects on the myocardium because of a shorter interdialysis period thus reduced fluid accumulation. This can lead to normal extracellular fluid volume, so that blood pressure can be more normotensive<sup>37</sup>.

This study also showed improvement in patient adherence to medication measured by 4-item Morisky scale. This result corresponded to one of patient education and counseling objectives, that was improving patient adherence to medication<sup>7</sup>.



Pharmacist counseling might improve patients understanding of the need to properly take their medications and this became an inception to motivate patients to adhere to their medication. Thus, the reinforcement of patients adherence to medication might improve patient's clinical outcome, as shown in this study.

Since volume overload has an important role in the pathogenesis of hypertension in hemodialysis patients and volume control in hemodialysis patients improves blood pressure control, this study evaluated patient IDWG as a parameter of patient adherence to sodium and water restriction. This study found no difference in IDWG in the intervention as well as the control group between pre and posttest measurement. This study also found that patients had well controlled IDWG. In patients with good adherence to strict salt restrictions, the interdialysis weight does not exceed 2 kg (3% of dry weight)<sup>38</sup>.

In this study, counseling session discovered problems occurred that causing hypertensive hemodialysis patients were failed to take their medication such as the symptomless nature of the condition, complicated medication regimen, side effect and long duration of medication, medication supply, cost of medication, the lack of patient understanding about hypertension management, and challenge to individual's belief about their illness and medication. Counseling is the opportunity to motivate patients to adhere to medication, dialysis schedule, restriction to fluid and salt, as those are important factors in blood pressure management in hemodialysis patients.

Several method were used for mitigation potential bias and the effect of confounding factors. To minimize selection bias, the study used participants assigning into control group from the same background (the same hemodialysis unit) and the same characteristics. Patients were divided into different groups based on their hemodialysis schedule to minimize communication between groups eg transferring information given in counseling group to control group. To minimize information bias, the data were measure and collected by nurses who were blinded to patients assignment group. The data collected by different personel from who analyze and intepret the data. The study used the control group to minimize the psychological

changes that change patient's behaviour because of being research participants. To minimize confounding bias, the study matched the demographic characteristics between groups. The study also took into account the effect of confounders in data analysis (by multivariate analysis) after data was collected.

## 5. CONCLUSIONS

Pharmacist counseling was the most determinant factor in lowering pre- and intradialysis blood pressure in the hypertensive hemodialysis patient

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### Conflict of interest (If any)

None to declare

### Funding

None to declare

### Ethical approval

This study was registered and approved by the Ethics Committee of Medicine Faculty of Universitas Indonesia (No.0347/UN2.F1/ETIK/2018) and Rumah Sakit Umum Pusat (RSUP) Fatmawati Jakarta (DM.01.01/VIII.2/4473/2018). Informed consent was given to subjects before sampling.

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