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A Combination of Hemodialysis with Hemoperfusion Helped to Reduce the Cardiovascular-Related Mortality Rate after a 3-Year Follow-Up: A Pilot Study in Vietnam

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Keywords
Parathyroid hormone · Mortality · Hemodialysis · Hemoperfusion

Abstract
Aims: Moderate to severe hyperparathyroidism (parathyroid hormone [PTH] concentrations ≥600 pg/mL) may increase the risk of cardiovascular problems and bone disease. We assume that a combination of hemodialysis with hemoperfusion may reduce the cardiovascular-related mortality rate in maintenance hemodialysis. ***Subjects and Methods:*** From 625 maintenance hemodialysis patients, 93 people met with our inclusion criteria. Based on the level of serum PTH, the patients were divided into 2 groups: 46 patients who underwent a combination of hemodialysis and hemoperfusion (HD + HP group) for consecutive 3 years and 47 patients who used hemodialysis only (HD group). ***Results:*** During 3 years of follow-up, the ratio of mortality was 4.3% in the HD + HP group which was significantly lower than in the HD group (17%), $p = 0.049$. Based on Kaplan-Meier analysis of cardiovascular-related mortality, patients in the HD group (red line) exhibited a significantly higher death rate compared to the HD + HP group (violet line) (log-rank test, $p = 0.049$). ***Conclusion:*** We demonstrated that a combination of hemodialysis and hemoperfusion for 3 years helped to reduce the cardiovascular-related mortality rate.

Introduction

Hemodialysis (HD) is the most common method used to treat advanced and permanent kidney failure globally including Vietnam [1]. The purpose of the method is that removing the harmful wastes and extra salt and fluids helps control the blood pressure of patients and keeps the proper balance of chemicals such as potassium and sodium in their body [2–4]. Based on molecular weight, the harmful wastes were divided into 3 groups: the wastes with low molecular weight, middle molecular weight substances, and high molecular ones [5–7]. HD with a low coefficient dialyzer (the most common one in Vietnam) could not clean middle and high molecular weight ones including cytokines, beta2-microglobulin (β2-M), and parathyroid hormone (PTH) [8–10].

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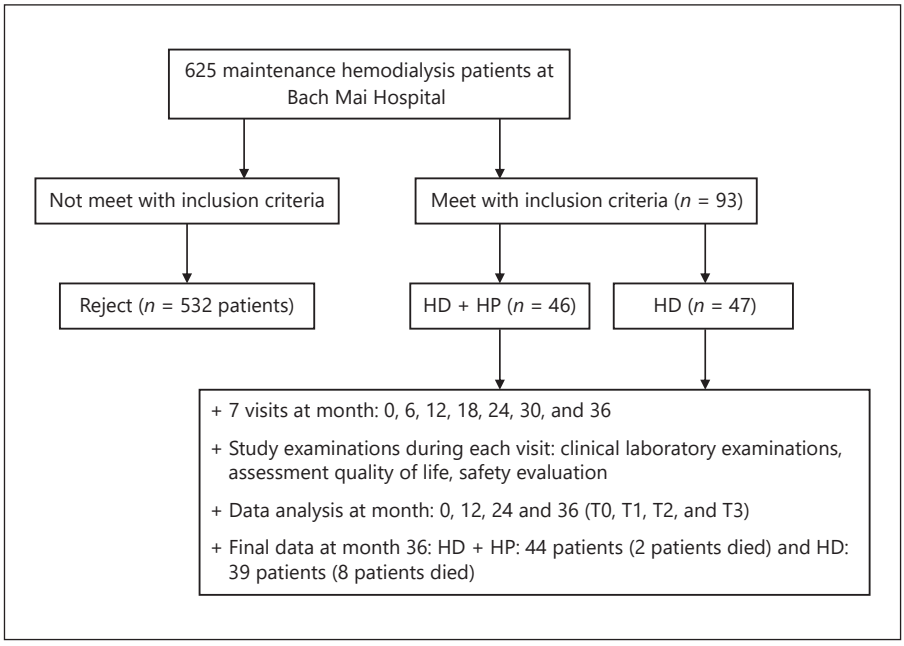

Fig. 1. Study design.

Hyperparathyroidism is a common complication of chronic kidney disease (CKD; nondialysis and dialysis) characterized by elevated PTH levels secondary to derangements in the homeostasis of calcium, phosphate, and vitamin D [11, 12]. Moderate to severe hyperparathyroidism (PTH concentrations ≥600 pg/mL) may increase the risk of cardiovascular problems and bone disease [13, 14]. The recommended target range for serum PTH in dialysis patients has changed from 150 to 300 pg/mL in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [15]. Hemoperfusion (HP) is a method carried out by using a special dialyzer and can combine with regular HD on a dialysis section. In recent years, HP technology has been widely used in many fields of clinical practice [16]. A number of studies have confirmed that HP can effectively remove PTH, β2-M, and other moderate and macromolecular weight uremic toxins [17]. To increase the quality of life in maintenance HD patients, we conducted a combination of HD with HP and follow-up for 3 years to know whether it may reduce the cardiovascular-related mortality rate.

Materials and Methods

Patients and Research Process

We included 625 patients with more than 3 months of maintenance HD duration using the low-flux dialyzer reused 6 times at Bach Mai Hospital, Ha Noi, Vietnam, into our study from March 2015 to March 2018. Substantive protocol amendments were reviewed and approved by the Ethical Committee of Bach Mai Hospital (No. 236/QĐ/BVBM). We excluded 532 patients with one or more of the following conditions: white blood cell count $<4 \times 10^9$/L (25 patients), platelet count $<100 \times 10^9$/L (34 patients), cerebral hemorrhage in the past 12 weeks (11 patients), active gastrointestinal bleeding (16 patients), coagulation dysfunction (35 patients), acute infection (141 patients), malignancy (8 patients), severe heart or liver failure (17 patients), not followed up for 3 years, or not using a combination of maintenance HD with HP for 3 consecutive years (245 patients). The remaining 93 maintenance HD patients gave written informed consent prior to participation in our study.

We divided 93 patients into 2 groups: one group with a combination of hemoperfusion and maintenance hemodialysis (HD + HP, $n = 46$) and the other group with hemodialysis alone (HD, $n = 47$). The enrolled patients have treated 3 sessions weekly with the low-flux reuse dialyzer to reach the target of total Kt/V, which was calculated as the formula of Daugirdas [18], more than 1.2 per session. We asked and examined patients to determine the cause of kidney failure, symptom of shoulder pain, carpal tunnel syndrome, itchy state, and quality of life by Short Form 36 (SF-36).

The primary outcome of the HD + HP versus HD trial was to test if HD + HP treatment was superior to regular HD alone in reducing cardiovascular-related mortality in HD patients. Cardiovascular cause mortality in our patients was defined as death attributable to myocardial ischemia and infarction, heart failure, cardiac arrest, or cerebrovascular accident [19]. The secondary outcome was to test if HD + HP treatment was superior to regular HD treatment in terms of improving the quality of life as well as anemia state. Our research process was carried out as described in Figure 1.

Treatment

Patients of the control group (HD group) received low-flux HD treatment at a frequency of 3 times a week, with each treatment session lasting 4 h. In the study group (HD + HP group), apart

Table 1. Comparison of clinical characteristics and laboratory parameters between 2 groups (n = 93)

	Both groups (n = 93)	HD + HP (n = 46)	HD (n = 47)	p values
Ages, years	55 (40.5–66)	51.5 (36.75–66)	56 (43–66)	0.468
Male, n (%)	57 (61.3)	23 (50)	34 (72.3)	0.027
Duration of hemodialysis, month	27 (11.5–67)	30.5 (11.75–67.5)	27 (11–62)	0.932
BMI	20.86±2.5	20.9±2.88	20.81±2.09	0.867
Hypertension, n (%)	69 (74.2)	34 (73.9)	35 (74.5)	0.951
Itchy symptoms, n (%)	52 (55.9)	25 (54.3)	27 (57.4)	0.763
Pain of shoulder and bone, n (%)	32 (34.4)	17 (37)	15 (31.9)	0.609
Carpal tunnel syndrome, n (%)	23 (24.7)	12 (26.1)	11 (23.4)	0.764
SF-36	37 (26.33–52.7)	38.8 (25.28–53.28)	36.5 (27.3–52.5)	0.954
Etiology, n (%)				
CGN	59 (63.4)	36 (78.3)	23 (48.9)	0.044
Diabetic nephropathy	12 (12.9)	4 (8.7)	8 (17)	
Chronic pyelonephritis	11 (11.8)	4 (8.7)	7 (14.9)	
Hypertension	9 (9.7)	2 (4.3)	7 (14.9)	
Others	2 (2.2)	0 (0)	2 (4.3)	
Residual kidney function, n (%)	27 (29)	14 (30.4)	13 (27.7)	0.768
HBV and/or HCV (+), n (%)	35 (37.6)	17 (37)	18 (38.3)	0.894
Lipid disorder, n (%)	50 (53.7)	24 (52.2)	26 (55.3)	0.761
Urea, mmol/L	25.9±7.46	26.65±8.01	25.16±6.89	0.339
Creatinine, μmol/L	902 (749.5–1,104.05)	946 (760.25–1,070.37)	877 (715–1,114)	0.659
Albumin, g/L	37.74±4.09	38.18±4.19	37.32±3.98	0.313
Hs-CRP, mg/L	0.4 (0.25–0.6)	0.55 (0.2–0.8)	0.4 (0.3–0.6)	0.487
Hemoglobin, g/L	100.92±13.44	102.33±14.6	99.55±12.2	0.323
Anemia, n (%)	55 (59.1)	21 (45.7)	34 (72.3)	0.009
β2-M, mg/L	26.66 (25.38–52.28)	28.16 (26.09–51.7)	26.44 (24.98–54.3)	0.265
PTH, pg/mL	267.5 (167.85–823.4)	823.4 (673.55–1,087.58)	167.9 (126.6–211.1)	<0.001
Calcium, mmol/L	2.27±0.26	2.3±0.31	2.24±0.19	0.316
Phosphate, mmol/L	1.91±0.66	2.06±0.73	1.76±0.54	0.031
Cardiovascular-related mortality after 3 years, n (%)	10 (10.8)	2 (4.3)	8 (17)	0.049

SF-36, Short Form 36; CGN, chronic glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; hs-CRP, high-sensitive C-reactive protein; β2-M, beta2-microglobumin; PTH, parathyroid hormone.

from treatments such as those of the HD group, HP was conducted 1 time/week for the first month, 2 times/the second month, and 1 time/month from the third month to the endpoint of the study (36 months) using a HA 130 resin HP apparatus containing 130 mL resin (following the guideline of product company: Zhuhai Jafron Biomedical, China).

During the treatment session, patients received HD + HP for the first 2 h using an HA 130 resin HP apparatus containing 130 mL resin (Zhuhai Jafron Biomedical, China) and the blood flow rate was maintained between 150 and 200 mL/min. After 2 h, when the HP apparatus was depleted, the HP cartridge was removed and the blood went through the low-flux HD dialyzer alone for the rest 2 h with the blood flow rate between 250 and 300 mL/min. The dialyzate flow rate was 500 mL/min. Heparin with a dose of 0.3–0.5 mg/kg at the first 10 min and maintaining 4–6 mg/30 min until the end of the treatment session was used.

Biochemical Assays and Other Measurements

Blood was drawn just before the start of a dialysis session in a nonfasting state to measure serum albumin, creatinine, blood urea nitrogen, C-reactive protein (CRP), and hematocrit once a month as routine clinical care which was performed in almost all dialysis centers in Vietnam. Serum PTH and β2-M concentration was measured using the latex immunoassay principle at the time of enrollment.

Serum PTH and other substances were measured before dialysis session (after 2 h of performing HP and after 4 h of dialysis session) at month 0, 12, 24, and 36 (T0, T1, T2, and T3). We also interviewed patients to get a result of the quality of life by SF-36 at the abovementioned points.

Statistical Methods

All normally distributed and continuous data are represented as mean ± SD and were analyzed using Student's t test. All the nonnormally distributed data are represented as median (25–75 percentile) and were analyzed using the Mann-Whitney U test. Categorical data are presented as the frequency with percentage and were analyzed using the χ^2 test. Survival curves were assessed using the Kaplan-Meier analysis and evaluated using the log-rank test. Statistical analysis was performed using the Statistical Package for the Social Sciences version 20.0 (Chicago, IL, USA). A p value <0.05 was considered significant.

Table 2. Comparison of results after the first hemodialysis session between 2 groups

	HD + HP (n = 46) (1)		HD (n = 47) (2)		p values
	before (a)	after (b)	before (c)	after (d)	
WBC, G/L	6.58±1.57	6.38±1.55	6.37±1.55	6.13±1.64	a–b = 0.143, c–d = 0.052, a–c = 0.515, b–d = 0.464
RBC, T/L	3.52±0.46	3.58±0.53	3.5±0.38	3.54±0.37	a–b = 0.037, c–d = 0.116, a–c = 0.839, b–d = 0.665
Hb, g/L	102.33±14.6	101.96±13.35	99.55±12.2	99.45±11.94	a–b = 0.593, c–d = 0.848, a–c = 0.323, b–d = 0.342
Urea, mmol/L	26.65±8.01	9.83±3.23	25.16±6.89	10.02±1.53	a–b < 0.001, c–d < 0.001, a–c = 0.339, b–d = 0.717
Creatinine, μmol/L	946 (760.25–1,070.37)	321.3 (237.05–345.82)	877 (715–1,114)	321.4 (234.1–432.1)	a–b < 0.001, c–d < 0.001, a–c = 0.659, b–d = 0.966
Calcium, mmol/L	2.3±0.31	2.59±0.23	2.24±0.19	2.56±0.12	a–b < 0.001, c–d < 0.001, a–c = 0.313, b–d = 0.501
Phosphate, mmol/L	2.06±0.73	1.00±0.28	1.76±0.54	1.75±0.51	a–b < 0.001, c–d = 0.554, a–c = 0.031, b–d < 0.001
β2-M, mg/L	28.16 (26.09–51.7)	25.72 (21.3–48.13)	26.44 (24.98–54.3)	26.55 (24.98–55)	a–b < 0.001, c–d = 0.43, a–c = 0.265, b–d = 0.202
PTH, pg/L	823.4 (673.55–1,087.58)	557 (450.7–795.12)	167.9 (126.6–211.1)	167.9 (132.4–213.2)	a–b < 0.001, c–d = 0.19, a–c < 0.001, b–d < 0.001

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; β2-M, beta2-microglobumin; PTH, parathyroid hormone.

Color version available online

Fig. 2. Changes of serum PTH and β2-M of 2 groups according to time (T0, T1, T2, and T3).

Results

The baseline demographic and laboratory characteristics in patients are shown in Table 1. In our study, we found the only difference in the rate of anemia and the mean level of serum phosphate between HD + HP and HD groups, $p < 0.05$. The median serum PTH level in the HD + HP group was higher than that in the HD group, $p < 0.01$. Especially, the ratio of mortality after a 3-year follow-up in the HD + HP group was lower than that in the HD group, $p < 0.05$.

Table 2 shows that there was a significant decrease in serum phosphate, β2-M level, and PTH as well as urea and creatinine concentration in the HD + HP group compared with those of the HD group, $p < 0.001$. However, there was no difference in levels of the abovementioned substances before and after a session in the HD group. We did not find any difference in the number of WBC, RBC, and Hb between 2 groups after a HD session.

In the HD + HP group, there was a significant reduction in the level of not only PTH but also serum β2-M, $p < 0.01$. In contrast, in the HD group, there was a significant increase in serum PTH and β2-M levels after 1, 2, and 3 years, $p < 0.01$ (Fig. 2).

The combination of HD + HP resulted in good outcomes such as the lower ratio of mortality, reduction in

Table 3. Comparison of clinical characteristics and laboratory parameters of 2 groups after 3 years

	HD + HP (1)		HD (2)		*p* values
	T0 (*n* = 44)	T3 (*n* = 44)	T0 (*n* = 39)	T3 (*n* = 39)	
Hypertension					
n (%)	30 (68.18)	26 (59.09)	28 (71.79)	26 (66.67)	pT3 (1–2): 0.327
p values		0.342		0.631	
BMI					
Mean	20.89±2.92	21.45±2.04	20.79±2.06	20.31±1.79	pT3 (1–2): 0.011
p values		0.009		0.002	
Itchy symptoms					
n (%)	22 (50)	10 (22.72)	22 (56.41)	25 (64.1)	pT3 (1–2): 0.001
p values		0.007		0.479	
Pain of shoulder and bone					
n (%)	15 (34)	6 (13.63)	10 (25.64)	18 (46.15)	pT3 (1–2): 0.003
p values		0.023		0.057	
Carpal tunnel syndrome					
n (%)	11 (25)	9 (20.45)	10 (25.64)	12 (30.76)	pT3 (1–2): 0.475
p values		0.607		0.613	
SF-36					
Median	41.3 (28.15–55.65)	44.4 (36–58.7)	39.15 (33.43–57.23)	38.05 (33.43–49.83)	pT3 (1–2): 0.01
p values		<0.001		0.008	
Lipid disorder					
n (%)	25 (56.81)	27 (61.36)	23 (58.97)	24 (61.53)	pT3 (1–2): 0.802
p values		0.646		0.813	
Albumin, g/L					
Mean	38.71±3.56	39.16±3.96	38.73±3.1	38.24±3.56	pT3 (1–2): 0.160
p values		0.423		0.336	
Anemia					
n (%)	36 (81.81)	32 (72.72)	32 (82.05)	34 (87.17)	pT3 (1–2): 0.171
p values		0.240		0.497	
Hemoglobin, g/L					
Mean	99.5±18.59	103.19±18.32	100.78±16.97	96.28±19.22	pT3 (1–2): 0.025
p values		0.211		0.097	
β2-M, mg/L					
Median	27.2 (26.05–48.53)	16.7 (14.5–21.52)	26.25 (24.2–27.02)	48.9 (45.6–65.4)	pT3 (1–2): <0.001
p values		<0.001		<0.001	
PTH, pg/mL					
Median	823.4 (669.45–1,071.32)	132.45 (121.87–204.77)	167.8 (126.6–211.1)	456.1 (345.9–459.9)	pT3 (1–2): <0.001
p values		<0.001		<0.001	
Phosphate, mmol/L					
Mean	2.07±0.74	0.92±0.16	1.73±0.55	1.81±0.40	pT3 (1–3): <0.001
p values		<0.001		0.04	
Calcium, mmol/L					
Mean	2.32±0.27	2.68±0.13	2.25±0.19	2.61±0.11	pT3 (1–3): 0.01
p values		<0.001		<0.001	

SF-36, Short Form 36; β2-M, beta2-microglobumin; PTH, parathyroid hormone.

itchy symptoms, reduction in the shoulder and bone pain, decrease in the level of phosphate, and increase in BMI, quality of life, and serum calcium level, $p < 0.05$ (Table 3). Kaplan-Meier analysis of cardiovascular-related mortality was classified according to HD with and without HP (red line: HD group; violet line: HD + HP group). Patients in the HD group (red line) exhibited a significantly higher death rate compared with the HD + HP group (violet line) (log-rank test, $p = 0.049$).

Discussion

High Serum PTH Predicts Mortality in Maintenance Hemodialysis

The increase in serum PTH was common not only in HD patients but also in CKD patients [20–23]. In our study, the median concentration of serum PTH was 267.5 pg/mL (Table 1). PTH reflects the function of the parathyroid gland and also primarily takes part in the metabolism of calcium, phosphate, FGF23 (fibroblast growth factor 23), and vitamin D. Enhanced PTH secretion occurs in response to hypocalcemia, hyperphosphatemia, and/or a decrease in serum 1,25-dihydroxy vitamin D ($1,25[OH]_2D$) level, whereas high serum levels of calcium, calcitriol, or FGF23 suppress PTH secretion. The extracellular concentration of ionized calcium is the most essential determinant of the minute-to-minute oscillatory secretion of PTH, which tends to be blunted in CKD patients [24]. Once secreted, PTH is rapidly cleared from plasma through cellular uptake principally by the liver and kidneys, where PTH undergoes intracellular proteolysis into active amino- and inactive carboxyl-terminal PTH fragments. The fate of these 2 types of PTH fragments is different: the N-terminal PTH fragments are rapidly degraded in situ by the liver and kidney, whereas the carboxyl-terminal (C-terminal) PTH fragments are mainly released into the blood and eventually excreted by the kidney.

With the progression of CKD, phosphate is retained due to decreased urinary phosphate excretion. However, hyperphosphatemia usually does not become evident before stage 4 CKD. In this study, we found an increase in serum phosphate levels in patients with maintenance HD. The mechanisms how phosphate retention contributes to the development of secondary hyperparathyroidism are multifactorial [25], including the induction of hypocalcemia, diminished renal production of $1,25(OH)_2D$ by inhibiting 1-alpha-hydroxylase activity, increased PTH gene expression by reducing PTH mRNA degradation, direct stimulation of parathyroid growth, and stimulation of FGF23 production in bones. Our patients' group had a median duration of HD of 27 months, with many symptoms of hyperparathyroidism including body aches, bone pain, depression, and low quality of life (Table 1).

CKD patients with elevated PTH resulting from secondary hyperparathyroidism have been shown to be at higher risk for cardiovascular morbidity and mortality. In our study, the ratio of cardiovascular-related mortality after 3 years of follow-up in patients with a combination of HD + HP was only 4.3% while that of patients with HD was 17% ($p = 0.049$). This might be explained by the HD + HP group had a lower level of serum PTH than the HD group (127.3 vs. 443.2 pg/mL, $p < 0.0001$; Fig. 2). A reduction in serum PTH resulted in low mortality ratio. There were also several mechanisms that may explain the link between PTH and cardiovascular mortality in our study. First, PTH has been directly implicated in atherogenesis via vascular calcification and vascular remodeling [26, 27]. Second, PTH appears also to have detrimental effects on the myocardium via induction of left ventricular hypertrophy and cardiac calcification. Higher PTH is associated with both established cardiovascular risk factors and more recently described risk factors such as inflammation markers [28–30]. Finally, because PTH is one of the key regulatory hormones in the mineral homeostasis, it is possible that the plasma levels of PTH reflect other abnormalities along the same pathway such as vitamin D deficiency, hypercalcemia, hyperphosphatemia, or renal failure that predispose to a higher risk for cardiovascular mortality [28–30]. The recommended target for serum PTH in dialysis patients has changed below 300 pg/mL in the KDOQI guidelines [15].

Combination of Hemodialysis with Hemoperfusion to Reduce the Cardiovascular-Related Mortality Rate

Dietary control, phosphate binders, and active vitamin D analogs are used in earlier secondary hyperparathyroidism. For maintenance HD patients, using a special dialyzer to clean PTH is necessary. Because PTH and β2-M are mildly molecular substances, dialysis with high-flux dialyzers or hemodiafiltration online or HP is effective. Vietnam Health Ministry encourages using a new method to improve the quality of life for maintenance HD patients. HP was used for patients with the concentration of serum PTH >600 pg/mL in Vietnam since 2012. We designed the study with 93 patients, who were divided into 2 groups: the HD + HP group with a level of serum PTH > 600 pg/mL (patients with HP indication based on the Vietnam Health Ministry guideline) and the HD group with a level of serum PTH < 300 pg/mL. After 3 years of follow-up, the results showed that HD + HP improved symptoms of secondary hyperparathyroidism such as reduction in itchy symptoms, reduction in the pain of shoulder and bone, and decreasing level of serum phosphate,especially improved quality of life (SF-36 better compared with the HD group) and improved BMI in hemodialysis patients (Table 3). In the hemoperfusion method, in addition to reducing the concentration of plasma PTH, this method also reduces other substances such as β2- MG, cytokine, phosphor, and substances with

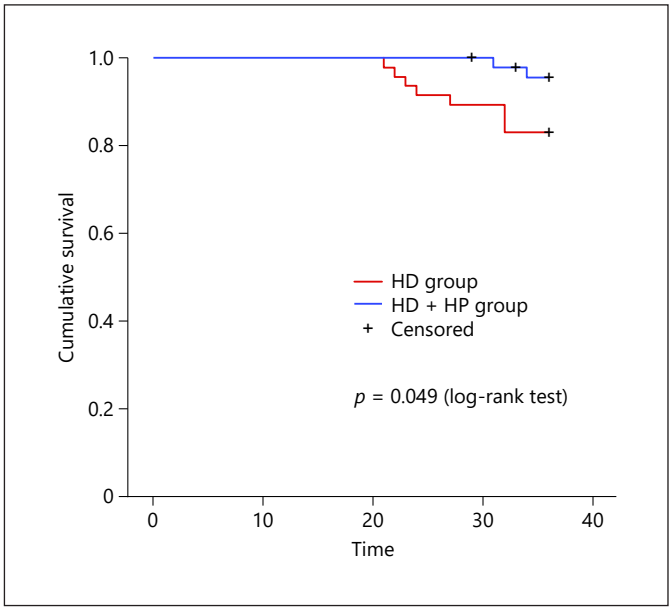

Fig. 3. Kaplan-Meier analysis of cardiovascular-related mortality, classified according to hemodialysis with and without hemoperfusion (red line: HD group; violet line: HD + HP group). Patients in the HD group (red line) exhibited a significantly higher death rate compared with the HD + HP group (blue line) (log-rank test, $p = 0.049$).

average molecular weight, thereby reducing the events related to increasing the concentration of these substances such as kidney bone disease, renal neuropathy, and cardiovascular events.

After 3 years, there were 2 dead patients (4.3%) in the HD + HP group, while the mortality rate of the HD group was 17% (Table 1). The HP method helped to reduce PTH and β2-M levels and did not affect the effectiveness of urea and creatinine filtration in maintenance HD patients. The reduction in urea and creatinine concentration was found, and the hematological indices did not change after each dialysis session (Table 2). Some previous studies showed that long-term combination of hemodialysis and HP effectively improved uremia complicated with bone and mineral disorders [31] and also improved sleep and increased the overall survival [32]. The results of our study once again confirmed that the combination of HD and HP reduced the manifestations related to calcium, phosphates, and PTH metabolic disorders and especially reduce the death rate due to cardiovascular events. A study of Gao et al. [33] showed that iPTH, β2-M, and cystatin C (CysC) levels were significantly lower in the HD + HP group than in the HD group ($p < 0.05$), and iPTH levels were significantly higher than those at the first day after treatment ($p < 0.05$). Kaplan-Meier analysis of cardiovascular-related mortality was classified according to HD with and without HP (red line: HD group; violet line: HD + HP group). Patients in the HD group (red line) exhibited a significantly higher death rate compared with the HD + HP group (violet line) (log-rank test, $p = 0.049$) (Fig. 3).

We initially designed 100 patients per group; however, during 3 years of follow-up and treatment of patients, lots of patients did not perform adequate filtration according to the instructions and some patients transferred to other dialysis centers, so the number of patients in the 2 groups remained 93. The small number of patients was the limitation of this study.

Conclusion

We demonstrated that a combination of HD and HP for 3 years reduced the cardiovascular-related mortality rate.

Acknowledgement

We would like to express our gratitude to all doctors and staff in the Hemodialysis Department, Bach Mai Hospital, who participated in this study.

Statement of Ethics

Substantive protocol amendments were reviewed and approved by the Ethical Committee of Bach Mai Hospital (No. 236/QĐ/BVBM) to ensure adherence to the guidelines of Good Clinical Practice of Vietnam Health Ministry. No animal was used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All patients had given written informed consent prior to participation in our study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Nguyen Huu Dung and Dao Bui Quy Quyen: research idea and study design. Nguyen Thi Thu Hai and Phan The Cuong: data acquisition. Nguyen Duc Loc: data analysis/interpretation. Nguyen Thi Hong Quyen: statistical analysis. Do Quyet and Le Viet Thang: supervision or mentorship.

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