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Additional hemoperfusion is associated with improved overall survival and self-reported sleep disturbance in patients on hemodialysis

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Abstract

Introduction: Patients with maintenance hemodialysis have experienced long-standing sleep disturbance. In this study, we attempted to explore whether long-term hemoperfusion could improve sleep and increase the overall survival in hemodialysis patients.

Methods: A total of 158 patients, who underwent routine hemodialysis, were assessed in this study. These patients were computer-matched into two groups, with one group including 80 patients with absolute hemodialysis and the other consisting of 78 cases with hemodialysis in combination with hemoperfusion. Hemoperfusion was performed 1–2 times biweekly, with each session lasting 2 h. Self-reported sleep disturbance was evaluated before and after the observational time (2-year period); sleep quality was measured using the Pittsburgh Sleep Quality Index.

Findings: Using multivariate regression analyses, we found sleep duration was associated with age, diabetes, low income, pruritus, hyperphosphatemia, hypercalcemia, high parathyroid hormone, and hemoglobin ($P < 0.001$). The overall survival rate of the hemodialysis in combination with hemoperfusion group was significantly higher than that of the absolute hemodialysis group ($P < 0.05$) after adjusting for sex, age, and diabetes. A 2-year hemoperfusion therapy was associated with improved sleep disturbance and sleep efficiency; this was accompanied by an increase in nocturnal melatonin levels. Furthermore, there was a significant difference in the first hospitalization between the hemodialysis and hemodialysis in combination with hemoperfusion groups ($P < 0.01$).

Discussion: Our results indicated that hemoperfusion in combination with hemodialysis is associated with an increase in the overall survival and improved sleep disorders in hemodialysis patients.

Keywords

Hemodialysis, hemoperfusion, sleep disturbance, overall survival

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Introduction

Patients with end-stage renal disease (ESRD) under maintenance hemodialysis (HD) are at high risk of various complications, such as cardiovascular disease, bleeding and ischemic stroke, hypertension, and bone mineral metabolic disorders.[1–3] Most patients with maintenance HD also suffer from sleep disturbance. It has been reported that up to 80% of patients with chronic kidney disease (CKD) have subjective sleep complaints. These patients have short, fragmented sleep with a total duration of sleep in the range of 260–360 min, and sleep efficiencies ranging from 66% to

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85%.[4] Sleep is likely affected by factors such as uremia toxin, pruritus, as well as social and financial challenges.[5,6] Poor sleep quality, in addition to insufficient sleep, can reduce the overall quality of life and may lead to a host of other complications, including an impaired immune system, risk of cardiovascular disease, and even death.[7,8] Sleep disturbance can destroy the spirit and may even lead to suicide in HD patients. Currently, there is no efficient treatment approach for these patients. Hemoperfusion (HP) has been reported to improve some metabolic parameters, as well as increase comfortability in patients with HD.[9,10] However, the role of HP on improving sleep quality, as well as enhancing overall survival in these patients, should be further investigated. In this study, we explored whether long-term HP in combination with HD is associated with improved survival as the main outcome, and sleep disorders as the secondary outcome in HD patients.

Methods

Study patients

A total of 158 patients who underwent routine HD at Shanghai Pudong Hospital (Fudan University Pudong Medical Center, Shanghai, China) between May and June 2015 were included in this study. The inclusion criteria were as follows: (1) duration of maintenance HD of at least 3 months, and (2) patients were 18 years or older. Patients were excluded if (1) they were diagnosed with malignant tumors, an active rheumatism, infectious disease, or severe heart failure, (2) they would not consent to the study, (3) they received a poor short-term prognosis, (4) they were over 80 years old, and (5) there was a confirmed or suspected clinical diagnosis of obstructive sleep apnea. The study was approved by the Ethical Committee of Shanghai Pudong Hospital (Fudan University Pudong Medical Center, Shanghai, China). All patients provided informed consent and experiments were performed in accordance with the Ethical Committee's guidelines and regulations.

In this study, 78 patients with HD + HP were assessed, and 80 patients were matched for age and sex as control HD patients who were identified using electronic records. HP was performed 1–2 times biweekly (9 in 1 time/weekly; 69 in 1 time/biweekly), and each session lasted for 2 h. The HD + HP procedure was as follows: on the routine HD procedure, an HP cartridge was cascaded into the circulation. During the first 2 h, HD and HP proceeded simultaneously. After 2 h, the conventional HD continued for an additional 2 h following the removal of the HP cartridge. An HP cartridge (HA 130, resinous material, produced by Jafron Biomedical Co. Ltd, Zhuhai, Guangdong Province, China) was used in each treatment session. All patients underwent HD three times/per week, and each dialysis session was 4 h.

Study main outcome. The main outcome in this study was overall survival in two cohorts over a 2-year observable period.

Secondary outcome. The secondary outcome of this study was improvement of sleep disorders between the two groups.

Sleep duration and sleep quality assessment

Self-reported sleep disturbance was assessed before and after the observational time (2-year period) based on the National Sleep Foundation's adult sleep time duration recommendations, which classifies normal sleep as a duration between 7 and 8 h and a short sleep as a duration of less than 7 h.[11] Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). Sleep efficiency (%) was calculated as the ratio of sleep duration to total time in bed and was multiplied by 100, in which a sleep efficiency of 85% was considered good quality.[11]

Measuring parameters

The clinical characteristics and experimental data for each patient (i.e. C-reactive protein (CRP), albumin, hemoglobin, calcium, phosphorus, and intact parathyroid hormone (iPTH)) were collected before and after 2-year HP treatment. Blood samples were collected before dialysis session. The pruritus score was used to evaluate the probable effects on itching intensity using a Worst Itching Intensity Numerical Rating Scale (NRS) (range, 0–10; anchors at 0 "no itching"; 4–6 "moderate itching"; and 10 "worst possible itching").[12] In addition, a low-income family (%) refers to a family that earns less than 5000 RMB/month according to an economic report released by the government of China for Shanghai city. Meanwhile, we recorded the first hospitalization and deaths during the 2-year period.

Melatonin test

Plasma melatonin levels were evaluated using an enzyme-linked immunosorbent assay (ELISA) Kit (R&D Systems, MN, USA). Melatonin levels were collected at night (around 10:00 p.m., post-dialysis) before and after during 2-year follow-up period.

Statistical analysis

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., NC, USA) and the collected data were expressed as mean ± standard deviation (SD). When data followed a normal distribution, they were analyzed using a t-test; otherwise, a Wilcoxon's signed rank test was used. The chi-square test was performed to

Table 1. Characteristics of the HD versus HD + HP groups at baseline and at the 2-year follow-up.

	Baseline		*P*	End of treatment		*P*
	HD	HD + HP		HD	HD + HP	
Patients (n)	80	78		68	75	
Age (years)	62.5 ± 11.5	63.9 ± 12.8	NS	64.1 ± 10.6	65.6 ± 11.8	NS
Male (%)	41.25	43.56	NS	42.65	41.33	NS
Diabetes (%)	40	39.74	NS	41.18	40.0	NS
HD duration (years)	4.4 ± 0.5	4.8 ± 0.6	NS	6.3 ± 0.7	6.5 ± 0.8	NS
Low-incomes (%)	28.75	14.10	<0.05	25.0	12.0	<0.05
Pruritus score	7.3 ± 1.5	7.2 ± 1.4	NS	7.2 ± 0.9	5.9 ± 1.1	<0.01
Sleep medication	37	34	NS	28	19	<0.05
Laboratory parameters						
CRP (mg/L)	13.1 ± 0.7	12.7 ± 0.8	NS	12.7 ± 0.5	9.6 ± 0.4	<0.01
Albumin (g/dL)	31.1 ± 1.5	31.0 ± 1.6	NS	30.0 ± 2.1	31.4 ± 1.5	NS
Hemoglobin (g/dL)	9.8 ± 2.3	9.2 ± 2.7	NS	10.6 ± 0.6	10.8 ± 0.7	NS
Hypercalcemia (%)	8.75	8.97	NS	8.82	1.33	<0.05
Hyperphosphatemia (%)	75.0	76.9	NS	63.2	42.7	<0.05
iPTH (pg/mL)	601 ± 23.9	607 ± 23.5	NS	618 ± 29.4	449 ± 27.3	<0.01
Sleep parameters						
Sleep duration (min)	360 ± 16.6	370 ± 15.1	NS	368 ± 25.2	418 ± 22.7	<0.05
Sleep efficiency (%)	76 ± 5.5	78 ± 6.9	NS	78.5 ± 5.4	88.2 ± 3.5	<0.01

HD: hemodialysis; HD + HP: hemodialysis in combination with hemoperfusion; CRP: C-reactive protein; iPTH: Intact parathyroid hormone. Pruritus score evaluated itching intensity using a Worst Itching Intensity Numerical Rating Scale (NRS, 0 (no itching) to 10 (worst possible itching)). Low-incomes (%) refer to <5000 RMB/month/total family. Sleep medication refers to benzodiazepine drugs.

examine associations between dependent and independent variables. Relationships between variables were examined using a Spearman's rank correlation coefficient as well as multivariate regression analysis. A Kaplan–Meier survival analysis and Cox regression method were used to analyze the overall survival rates. The competing risk model for the first hospitalization and death was established using R software (R i386 3.4.3). The level of significance was set at $P < 0.05$.

Results

Baseline clinical characteristics of HD patients

In this study, 158 patients (67 males and 91 females) were evaluated. The primary diseases in the HD group included 24 patients with chronic nephritis, 35 with diabetic kidney disease, 7 with hypertensive kidney disease, 6 with interstitial nephritis, 3 with polycystic kidney disease, 3 with obstructive nephropathy, 1 with lupus nephritis, and 1 with another disease. While in the HD + HP group, the primary diseases included 35 patients with chronic nephritis, 28 with diabetic kidney disease, 6 with hypertensive kidney disease, 4 with interstitial nephritis, 3 with polycystic kidney disease, 5 with obstructive nephropathy, and 2 with other diseases. Primary disease was not statistically significant between the two groups. As shown in Table 1, there were no obvious differences regarding baseline parameters in terms of age, sex, diabetes, duration of HD, pruritus score, CRP, albumin, hemoglobin, hypercalcemia, hyperphosphatemia, iPTH, sleep duration (minutes), and sleep efficiency (%) between the two cohorts. The only difference observed was family income, which is likely attributed to the reduced ability of low-income families to afford the high-cost of HP.

Single-factor correlation analysis of sleep duration with clinical parameters

As displayed in Table 2, sleep duration was negatively correlated with age, albumin, diabetes, hemoglobin, high iPTH, hypercalcemia, hyperphosphatemia, low-income, and pruritus.

Factors associated with sleep duration

After performing a multivariate regression analysis, the achieved results indicated a *P*-value of less than 0.001. In addition, sleep duration was correlated with age, diabetes, hemoglobin, high iPTH, hypercalcemia, hyperphosphatemia, low-income, and pruritus (see Table 3).

Improvement of clinic parameters and sleep quality with the combination of HP with HD

As shown in Table 1, compared with the HD group, the HP + HD group showed improvements in some clinical

Table 2. Correlation of sleep duration with clinical parameters.

	Sleep duration	
	R	*P*
Age	−0.2895	<0.0001
Albumin	−0.2248	0.0014
Sex	−0.1133	0.3168
C-reactive protein (CRP)	0.1154	0.1289
Diabetes	−0.5791	<0.0001
Hemoglobin	−0.5579	<0.0001
High parathyroid hormone	−0.5491	<0.0001
Hypercalcemia	−0.2383	0.0005
Hyperphosphatemia	−0.6439	<0.0001
Low-incomes	−0.2306	0.0007
Pruritus	−0.6091	<0.0001

$P < 0.05$, statistically significant.

Table 3. Multiple linear regression equation analysis of the relationship between sleep duration and clinic parameters.

	Sleep duration			
	Coef.	Std. err	t	$P>\|t\|$
Age	−1.2457	0.3985	−3.62	<0.001
Albumin	–	–	–	–
Diabetes	−7.4048	0.5409	−13.69	<0.001
Hemoglobin	−0.7886	0.1369	−5.76	<0.001
High parathyroid hormone	−0.2825	0.0194	−14.54	<0.001
Hypercalcemia	−3.5547	0.7354	−4.83	<0.001
Hyperphosphatemia	−6.1634	0.5389	−11.44	<0.001
Low-incomes	−0.3642	0.0672	−5.41	<0.001
Pruritus	−5.4773	0.4120	−13.30	<0.001

Coef.: coefficient; Std. err: standard error.
Total F = 996.98; $P > F = 0.0000$; R-squared = 0.9787; adjusted R-squared = 0.9777; $P < 0.05$, statistically significant; "–" indicates variables with $P > 0.05$.

parameters, such as pruritus score, CRP, hypercalcemia, hyperphosphatemia, and iPTH. Furthermore, 2-year HP therapy was associated with improved sleep disturbance as well as sleep efficiency.

Competitive analysis of the first hospitalization and death

During the 24-month follow-up period, a total of 51 patients were admitted (31 in the HD group; 20 in the HD + HP group, see Table 4). Fifteen patients died during the 24-month follow-up period (12 in the HD group; 3 in the HD + HP group). Considering a competitive risk between the first hospitalization and death, we employed a Gray's test to analyze that competitive risk. The results of Gray's test showed that there were significant differences between the rates of cumulative incidence of death and the first hospitalization in the HD + HP group compared to the HD group (see Table 5).

Table 4. The details of the reason of hospitalization in each group.

Reason	HD	HD + HP	N
Infectious diseases			
Pulmonary infection	11	7	18
Urinary tract infection	1	1	2
Catheter infection	2	0	2
Diabetic foot infection	1	1	2
Cardiovascular diseases	7	5	12
Cerebrovascular incidents	6	3	9
Gastrointestinal bleeding	1	0	1
Bone fracture	1	0	1
Severe anemia	0	2	2
Other unknown causes	1	1	2
N	31	20	51

HD: hemodialysis; HD + HP: hemodialysis in combination with hemoperfusion.

Survival analysis of HD patients

By the completion of the study on 31 June 2017, 15 patients had died as a result of the following: cardiovascular diseases (four patients), pulmonary infection (three patients), cerebrovascular diseases (four patients), malignant tumors (one patient), gastrointestinal bleeding (two patients), and another cause (one patient). Three of them (two died for cardiovascular diseases and one died for malignant tumors) were in the HD + HP group, and the rest belonged to the HD group. The Kaplan–Meier survival analysis and Cox regression method showed that the survival probability was different between the absolute HD and the HD + HP group ($P < 0.05$); the unadjusted and adjusted survival curves for sex, age, level of income, and coexistence of diabetes are shown in Figure 1(a) and (b).

Comparing nocturnal melatonin levels between the HD and HD + HP groups

In order to explore the potential mechanism of improved sleep by HP, the average levels of nocturnal melatonin were investigated at baseline and at the end of the study in the HD and HD + HP groups. First, it was revealed that the level of nocturnal melatonin was strongly associated with duration of sleep (see Figure 2(a)). Furthermore, as illustrated in Figure 2(b), there was no significant difference in the baseline nocturnal melatonin level in the two cohorts. After a 2-year follow-up period, the levels of nocturnal melatonin in the HD + HP group (126.8 ± 22.16 pg/mL) were higher than those of the HD group (89.55 ± 18.49 pg/mL; $P < 0.05$).

Table 5. The cumulative incidence rates of death and the first hospitalization in HD and HD + HP patients.

Gray test	STAT	*P*	Df (degree of freedom)
Death	5.846316	0.01560969	1
First hospitalization	4.154223	0.04195643	1

HD: hemodialysis; HD + HP: hemodialysis in combination with hemoperfusion.
A Gray test was performed on the cumulative incidence rates of death and indicated that death was a competing risk factor for the first hospitalization in HD and HD + HP group. $P < 0.05$, statistically significant.

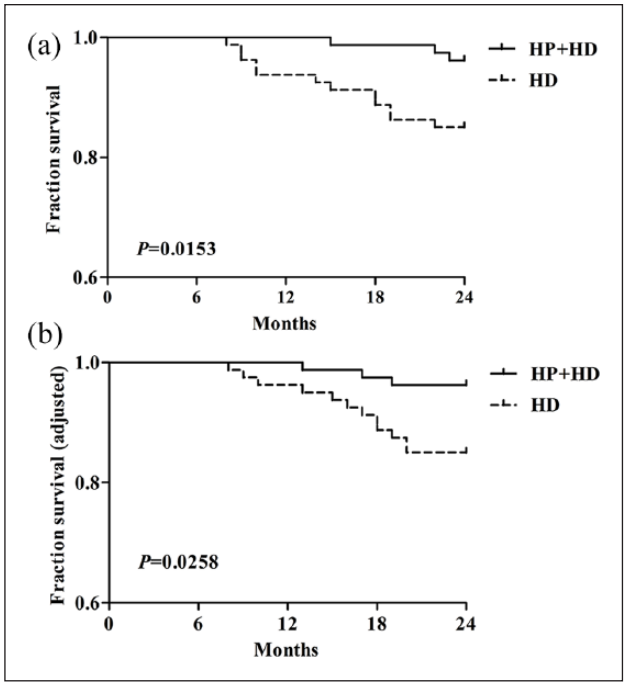

Figure 1. Kaplan–Meier survival curve in two cohorts after 24 months of observation unadjusted (a) and adjusted (b) survival curve for age, sex, coexistence of diabetes, and low-income.

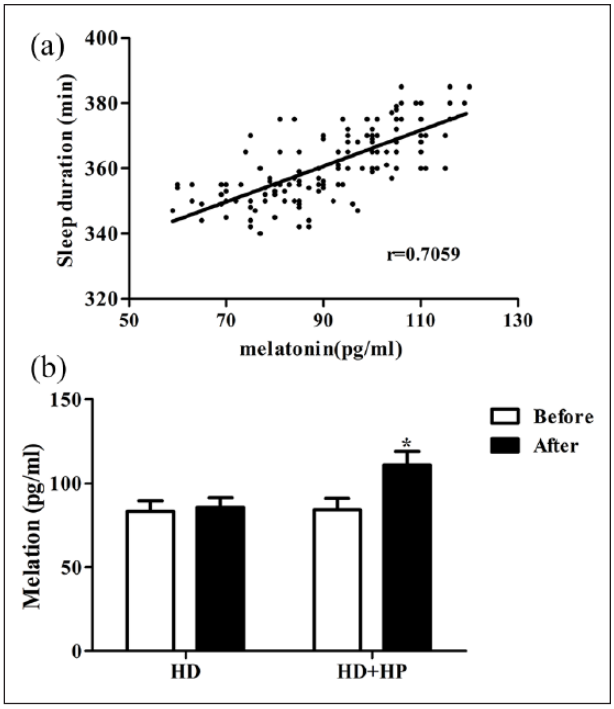

Figure 2. Nocturnal melatonin levels and effect of various treatment methods. A relationship between nocturnal melatonin level and sleep duration (a) Comparing nocturnal melatonin value between HD and HD + HP groups before and after 24-month follow-up period (b).
The symbol "*" denotes HD + HP group versus HD group ($P < 0.05$).

Adverse events

There were two cases in each group where a slight allergic reaction was observed at the beginning of the treatment period, and the symptoms disappeared after treatment for the reaction. No other adverse events occurred during the treatment period.

Discussion

Sleep disorders have a profound and well-documented impact on overall health and quality of life. In patients with CKD, especially those on HD, sleep disorders are more prevalent. Poor quality of sleep can lead to several complications, such as cardiovascular disease, and increased mortality in patients with ESRD under maintenance HD.[10] Factors associated with sleep disorders include uremic toxin, pruritus, abnormal mineral metabolism, and other unknown causes. It remains a challenge for nephrologists to determine how to solve sleep disorders and increase the rate of overall survival in patients. Non-pharmacological interferences, such as aerobic exercise, resistance training, acupuncture, electro-acupuncture, and acupressure, have been previously proposed; however, these interventions have shown negligible efficacy.[13,14]

Uremic pruritus has been associated with poor sleep quality.[15–18] Pruritus is a common and distressing symptom, affecting patients with CKD. The clinical presentation of pruritus in patients with CKD significantly varies from patient to patient. Treatment methods for pruritus are deficient or demonstrate little impact on local and systemic therapies. HP has been proposed to treat refractory pruritus in cholestatic liver disease, as well as refractory uremic pruritus.[19–21] In the present study, it was revealed that HP was associated with improved sleep duration,

accompanied with an improvement in pruritus. HP may better eliminate protein-bound uremic toxins than absolute HD, demonstrating that uremic toxins either in the central nervous system or peripherally may play a significant role in the pathophysiology of uremic pruritus.[22] However, it cannot be ruled out that HP has an effect on nociceptive sensory pathways in the peripheral and/or central nervous system.[17]

Renal replacement therapy modalities have been introduced to improve sleep disorders in a number of studies. Conventional renal replacement therapies have not had a significant impact on sleep disorders in patients with CKD.[5] Diminished health-related quality of life (HRQoL) is common in dialysis patients and is associated with increased risks of morbidity and mortality. Sleep disorders are typical manifestations of poor physical HRQoL in dialysis patients. In three randomized clinical trials, an intensive HD could increase Physical Component and Mental Health Component Summary scores derived from the 36-Item Short-Form Health Survey (SF-36)[23–25] compared to conventional HD. However, other trials and meta-analyses failed to prove these effective benefits of an intensive six-times-weekly daytime HD and/or prolonged daily nocturnal HD.[26–29]

Abnormal mineral metabolism, containing low and high serum calcium, phosphate, and parathyroid hormone levels, has been referred to as a potential cause of poor sleep in patients with HD. In the current study, sleep duration and efficiency were negatively associated with high serum calcium, as well as elevated levels of parathyroid hormone. These results are consistent with previous findings.[30] Improved sleep duration and efficiency in the HP group are likely due to the enhancement of mineral metabolism.

In order to explore the potential mechanism of improved sleep disorder in HP, we examined night blood melatonin levels. As expected, night melatonin levels were low in both the HD and HD + HP groups at the beginning of the study, but night melatonin secretion was increased by HP at the 2-year follow-up period, indicating that HP was associated with a remarkably recovered sleep-wake circadian rhythm. Melatonin, a hormone secreted by the pineal gland, is responsible for the sleep-wake circadian rhythm. It is secreted in small amounts during the day and is increased at night. Previous studies have shown that nocturnal melatonin levels were significantly lower in HD patients than in healthy participants.[31–33] Conventional HD did not improve melatonin concentrations, while nocturnal melatonin concentrations have also not improved following kidney transplantation despite recovery of renal function.[34] However, nocturnal melatonin levels were increased in HD patients after parathyroidectomy,[35] indicating that intact parathyroid hormone was likely associated with melatonin. This is a potential explanation for improved nocturnal melatonin secretion during HP therapy, due to the reduced parathyroid hormone levels after HP intervention, eventually leading to improvements in sleep duration and efficiency.

There were several potential limitations in this study. First, the duration of sleep and time in bed are self-reported; we do not use any instrument or method to precisely calculate sleep duration in HD patients. However, it is indeed difficult to obtain accurate sleep data in those patients, and thus, a self-reported method is highly recommended. Second, it is not a randomized, controlled trial, and an unavoidable selection bias exists. We used computer-matched HD controls to avoid selection bias, aiming to match the two groups to the same baseline. However, selection bias does exist due to the imbalance of household income between the groups. Third, we did not detect any dynamic variation in terms of night melatonin concentrations and daytime levels, except at 10:00 pm, which we believe they can reflect night melatonin levels. Fourth, laboratory values were only taken twice in a 2-year period, making it difficult to assess any evolution of those laboratory parameters. Future study may assess the dynamic change of those laboratory parameters during HP, especially a series of melatonin concentrations at different time points.

Conclusion

In summary, our results indicate that additional HP is associated with an increase in the overall survival rate and improved sleep disorders in maintenance HD patients, as well as reduces pruritus scores and parathyroid hormone as compared with HD alone. Also additional HP is associated with an increase in nocturnal melatonin concentration secretion, a sleep–wake circadian rhythm marker.

Declaration of conflicting interests

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