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ORIGINAL ARTICLE

Complications

Post-dialysis fatigue: Comparison of bicarbonate hemodialysis and online hemodiafiltration

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Abstract

Introduction: The present cross-sectional study aimed to compare the prevalence, the characteristics of post-dialysis fatigue and the length of recovery time after hemodialysis in prevalent end-stage renal disease patients (ESRD) receiving bicarbonate hemodialysis (HD) or hemodiafiltration (HDF).

Methods: Patients were suffering from post-dialysis fatigue if they spontaneously offered this complaint when asked the open-ended question: "Do you feel fatigued after dialysis?". Moreover, each patient was invited to rate the intensity, duration, and frequency of post-dialysis fatigue from 1 to 5. In order to assess RECOVERY TIME AFTER DIALYSIS, patients were invited to answer to the following single open-ended question: "How long does it take you to recover from a dialysis session?"

Findings: We included 335 patients: 252 received HD and 83 received HDF. Post-dialysis fatigue was present in 204 patients (60.9%). Prevalence of post-dialysis fatigue did not differ significantly between patients on HD (62.3%) and on HDF (56.6%; $p = 0.430$). Median recovery time after dialysis was 180 min [180–240] and did not differ significantly between the two subgroups (180 min [130–240] and 240 min [120–332] $p = 0.671$, respectively). Median post-dialysis fatigue intensity, duration, and frequency were 3 [1–5], 3 [1–5], and 4 [1–5] and did not differ significantly between patients on HD and on HDF. At the multivariate analysis, age, ADL and hemoglobin levels were the independent predictors of the HDF treatment.

Discussion: Prevalence and characteristics of post-dialysis fatigue do not differ significantly between patients receiving bicarbonate HD or HDF.

KEYWORDS

hemodialysis, online hemodiafiltration, post-dialysis fatigue, recovery time after hemodialysis

INTRODUCTION

End-stage renal disease (ESRD) patients on chronic hemodialysis frequently complain physical and emotional symptoms that reduce their quality of life.[1–8]

Post-dialysis fatigue is an especially distressing symptom, described as feeling tired and needing rest or sleep after the dialytic session. Other common descriptors of post-dialysis fatigue include being worn out or drained or exhausted.[9–15] The frequency of post-dialysis fatigue is high, ranging from 50.5% to 85%.[10–15] It seems that fatigue starts at the initiation of the dialytic session, progressively increases during the dialytic treatment and peaks at the end and in following hours.[16] Post-dialysis fatigue contributes to the length of the time of recovery after dialysis recovery time after dialysis. The etiology of post-dialysis fatigue is unknown, but there is some evidence that fatigue of patients on chronic hemodialysis is associated with increased serum levels of Interlukin-6 (IL-6) and other markers of chronic inflammation.[17–19]

Online hemodiafiltration (HDF) combines the benefits of diffusion and convection. It seems that online hemodiafiltration (HDF) improves the inflammatory state reducing the potential to produce pro-inflammatory cytokines by modulating the circulating levels of CD14+ CD16+ mononuclear cells.[20,21] Indeed, online hemodiafiltration is associated with significantly lower circulating levels of Interleukin-6.[22]

However, it remains unknown if HDF improves patients symptoms and fatigue[23–29] and there is lack of studies on the effect of HDF on post-dialysis fatigue prevalence and characteristics. In addition, data on the effect of HDF on the length of recovery time after dialysis are far to be conclusive.[30–32] The present cross-sectional study aimed to compare the prevalence and the characteristics of post-dialysis fatigue and the length of recovery time after dialysis in prevalent end-stage renal disease patients receiving bicarbonate hemodialysis (HD) or online hemodiafiltration (HDF).

PATIENTS AND METHODS

In the present cross-sectional study we collected demographic, clinical, and laboratory data of end-stage renal disease patients on chronic hemodialysis of five hospital hemodialysis units of our country. All prevalent chronic patients referring to these hemodialysis units in October 2021 were considered eligible. Exclusion criteria were as follows: dialysis duration <1 year, inability to answer the questionnaires because of hearing or reading problems, diagnosis of dementia based on DSM-IV criteria, presence of acute infectious disease(s), active cancer, or active cancer treatment. The study was conducted in adherence to the Declaration of Helsinki and the protocol was approved by the ethics committee of each of the participating centers (Protocols P/600/CE/2011/centers 1-5).

The following demographic, clinical, and laboratory data were recorded for each patient at the moment of the inclusion in the study: age, gender, primary cause of renal disease, dialytic age, weight, height, BMI, comorbidity through the Charlson comorbidity score index,[33] activity daily living (ADL),[34] instrumental activity daily living (IADL),[35] serum albumin, creatinine, hemoglobin, hematocrit, ultrafiltration rate, Na concentration in the dialysate, temperature of dialysate, and Kt/V.

Blood samples were obtained after overnight fasting from patients, through the arteriovenous fistula or the central venous catheter, immediately before their scheduled hemodialysis session, at the beginning of the week. Plasma samples were separated within 30 min, and frozen at −70 °C if not analyzed immediately. Laboratory parameters were measured by routine methods at the Department of Laboratory Medicine, Catholic University of Rome.

Type of hemodialysis

Patients were receiving conventional 4-h bicarbonate hemodialysis (HD) or online hemodiafiltration (HDF), three times a week. The dialysis treatment duration was 240 min. In HD, the blood flow ranged from 250 to 300 ml/min with a dialysis rate flow of 500 ml/min. In HDF, the blood flow ranged from 300 to 350 ml/min with a dialysis rate flow of 600 ml/min. All patients were treated with high-permeability membranes. Membranes were not reused. HDF was performed with a target convection volume of 22 L/treatment.

Assessment of PDF

The assessment of post-dialysis fatigue was conducted according to the recommendations by Sklar et al.[36–38] Patients were suffering from post-dialysis fatigue if they spontaneously offered this complaint when asked the open-ended question: “Do you feel fatigued after dialysis? If yes, then, each patient was invited to rate the intensity, duration, and frequency of post-dialysis fatigue from 1 to 5. Intensity was defined as the magnitude of fatigue, duration as the length of time that fatigue lasted, and frequency as the number of times that fatigue happened.

The recovery time after the hemodialysis session was calculated according to Lindsay et al.[39] Briefly, patients were invited to answer to the following single

TABLE 1 Comparison of characteristics of study participants. Data are shown as mean ± SD or median [95% CI for the median] or absolute numbers for categorical variables

	HD ($n = 252$)	HDF ($n = 83$)	p
Age (years)	70.4 ± 13.6	62.6 ± 14.1	<0.0001
Tukey 5-point percentiles	24-64-73-80-94	30-52-63-72-96	
Sex (F:M)	95:157	32:53	1.000
Dialytic age (months)	71.4 ± 73.6	84.8 ± 75.4	0.165
Primary cause of ESRD			0.455
Hypertension	81	20	
Diabetes	68	18	
Glomerulonephritis	24	11	
Polycystic renal disease	22	8	
Interstitial nephritis	20	7	
Other nephropaties	12	5	
Unknown	25	14	
Body mass index	24.5 ± 4.8	25.6 ± 6.8	0.181
Charlson comorbidity index	2 [2–12]	2 [1–2]	0.357
ADL score	6 [6–6]	6 [6–6]	0.018
IADL score	7 [6–7]	7 [6–8]	0.077
Serum albumin (g/dl)	3.62 ± 0.46	3.75 ± 0.42	0.045
Serum creatinine (mg/dl)	8.3 ± 2.4	9.3 ± 2.4	0.002
Hemoglobin (g/dl)	11.1 ± 1.1	11.6 ± 0.9	0.0006
Hematocrit (%)	34.4 ± 3.6	35.7 ± 3.1	0.008
Dialysate sodium (mEq/L)	139 ± 1.8	139.5 ± 1.5	0.098
Dialysate temperature (°C)	36.6 ± 0.4	36.7 ± 0.3	0.128
UFR (ml/kg/h)	9.08 ± 3	8.75 ± 3.3	0.408
Recovery time after dialysis (min) Tukey 5-point percentiles	15-60-180-480-1440	15-60-240-465-1440	0.671
Kt/V	1.46 ± 0.2	1.48 ± 0.3	0.487
Median	1.41	1.47	

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; TIRD, time of recovery after dialysis.

open-ended question: "How long does it take you to recover from a dialysis session?" Responses were subsequently converted into the number of minutes.

Statistical analyses

Statistical analysis was performed by using the Statistical Package for Social Science (SPSS), release 20.0. All data were first analyzed for normality of distribution using the Kolmogorov–Smirnov test of normality. Continuous variables were expressed as mean ± SD, categorical variables displayed as frequencies and the Mann–Whitney or X^2 nonparametric test were used to assess significance of the differences between subgroups. Multivariate binary logistic analysis, with stepwise regression, was performed to evaluate the relationship between the development of post-dialysis fatigue with HD type (bicarbonate hemodialysis vs. online hemodiafiltration) considering as confounding variables gender, age and ADL. The coefficients obtained from the logistic regression were expressed in terms of odds ratio with 95% confidence intervals. All of the tests were two-sided and statistical significance was set at $p < 0.05$.

RESULTS

Out of 335 patients included in the study, 252 received HD and 83 HDF. The characteristics of the two groups of patients are shown in the Table 1. Patients on online HDF were significantly younger and had significantly

TABLE 2 Multiple logistic regression

	$B \pm SE$	p	Odds ratio [95% CI]
Age (<65 vs. >65 years)	−1.131 ± 0.32	<0.001	0.32 [0.17–0.60]
ADL (score)	0.367 ± 0.184	0.047	1.44 [1.00–2.07]
Hb	0.332 ± 0.153	0.030	1.52 [1.14–2.02]

Note: Dependent variable: HD type.
Abbreviations: ADL, activities of daily living; Hb, hemoglobin.

TABLE 3 Characteristics of post-dialysis fatigue and type of dialysis

	HD ($n = 252$)	HDF ($n = 83$)	p
Post-dialysis fatigue intensity	3 [3–4]	3 [3–4]	0.303
Post-dialysis fatigue duration	3 [3–4]	3.5 [3–4]	0.869
Post-dialysis fatigue frequency	4 [4–4]	4 [4–4]	0.661
Post-dialysis fatigue Sum	11 [10–12]	11.5 [10–12]	0.957

higher serum albumin, creatinine, hemoglobin, and hematocrit levels. At the multivariate analysis, HDF treatment was significantly associated with age, ADL, and serum Hb levels (Table 2).

Post-dialysis fatigue was present in 204 patients (60.9%). The prevalence of post-dialysis fatigue did not differ significantly between patients on HD (62.3%) and patients on HDF (56.6%, $p = 0.430$). The median post-dialysis fatigue intensity was 3[1–5] and did not differ significantly between patients on HD and on HDF (Table 3). The median post-dialysis fatigue duration was 3[1–5] and was similar in patients on HD and on HDF (Table 3). The median post-dialysis fatigue frequency was 4[1–5] and did not differ significantly between patients on HD and on HDF (Table 3).

Then, patients were divided into two groups, one with post-dialysis fatigue and one without post-dialysis fatigue and compared (Table 4). Patients with post-dialysis fatigue were significantly older, had a lower ADL and were more frequently women. Accordingly, a significant difference in post-dialysis fatigue frequency between male and female subjects was observed (70% vs. 56%, $p = 0.012$); no incidence of HD type was detected (HD = 62%, HDF = 57%, $p = 0.358$).

Moreover, in Table 5 the entire and reduced model of the multivariate logistic regression is reported. In the final model, gender was the only variable independently associated with post-dialysis fatigue (OR 0.56 [0.34–0.910]; $p = 0.019$).

Despite not being the focus of the present manuscript, in order to verify the upper limit of prediction of the

TABLE 4 Comparison of characteristics of patients with and without PDF

	Post-dialysis fatigue absent ($n = 131$)	Post-dialysis fatigue present ($n = 204$)	p
Age (years)	66.4 ± 14.8	70.1 ± 13.3	0.021
Tukey 5-point percentiles	24-58-68-78-96	29-62-73-80-94	
Sex (F:M)	38:93	87:117	0.016
OLHDF, No. of patients (%)	34 (26.5)	49 (24.1)	0.714
Dialytic age (months)	74.4 ± 78.6	75.2 ± 71.7	0.926
Weight (kg)	69.4 ± 17.1	68.6 ± 16.1	0.683
Body mass index	24.2 ± 5.4	25.2 ± 5.3	0.158
Charlson comorbidity index	2 [0–7]	2 [0–8]	0.855
ADL score	6 [0–6]	5 [0–5]	0.012
IADL score	7 [0–8]	6 [0–8]	0.135
Serum albumin (g/dl)	3.66 ± 0.4	3.65 ± 0.4	0.840
Serum creatinine (mg/dl)	9.1 ± 2.4	8.6 ± 2.6	0.177
Hemoglobin (g/dl)	11.2 ± 1.1	11.2 ± 1.1	0.830
Hematocrit (%)	34.6 ± 3.4	34.8 ± 3.6	0.591
Dialysate sodium (mEq/L)	139.7 ± 1.7	139.8 ± 1.7	0.580
Dialysate temperature (°C)	36.6 ± 0.4	36.6 ± 0.4	0.859
UFR (ml/kg/h)	9.3 ± 3.2	9.02 ± 2.8	0.401
Qb (ml/min)	301.1 ± 14.6	301.9 ± 14.8	0.651

Note: Data are shown as mean ± SD or median [95% CI for the median] or absolute numbers for categorical variables.
Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living.

TABLE 5 Multiple logistic regression

Variable	$\beta \pm SE$	p	OR [95% CI]
Age (<65 vs. >65 years)	0.340 ± 0.264	0.197	1.40 [0.84–2.36]
ADL	−0.202 ± 0.103	0.050	0.82 [0.67–1.00]
Gender	−0.584 ± 0.248	0.018	0.55 [0.34–0.91]
HD type	−0.089 ± 0.282	0.751	0.92 [0.53–1.59]
Reduced model of the regression obtained with a backward-stepwise method			
ADL	−0.239 ± 0.101	0.018	0.79 [0.65–0.99]
Gender	−0.561 ± 0.246	0.023	0.57 [0.35–0.93]

Note: Dependent variable: PDF. Covariates: Clinical parameters.
Abbreviations: ADL, activities of daily living.

proposed reduced multivariate models (Table 5 for post-dialysis fatigue and Table 2 for HD type), we used the score generated for each patient by the specific model and the mean for the population as threshold, thus calculating the number of patients consistent with the prediction (i.e., if the observed and predicted classification was the same). We obtained, for HD type, an overall agreement of 70% (73% and 61% for HD and HDF, respectively) and, for post-dialysis fatigue, an overall agreement of 59% (65% and 55% for post-dialysis fatigue absent and post-dialysis fatigue present, respectively).

Median [95% CI for median] recovery time after dialysis was 180 min [180–240] and did not differ significantly between patients on HD (180 min [130–240]) and on HDF (240 min [120–332] $p = 0.671$).

DISCUSSION

The present study demonstrates that the prevalence of post-dialysis fatigue does not differ significantly between patients receiving bicarbonate hemodialysis or online hemodiafiltration, although patients receiving HDF were significantly younger, had a higher ADL score, and had higher serum Hb levels. To our knowledge, this is the first time that such results are reported in a large population sample. Indeed, in the study of Karkar et al., including 72 patients, 24 months treatment with high efficiency post-dilution HDF, compared with the high-flux-treated group, showed a better effect on post-dialysis fatigue (10 ± 9 vs. 61 ± 18; $p < 0.0001$). Assessment was based on patient's satisfaction level using modified questionnaire survey of the Kidney Disease Quality of Life-Short Form with a scale ranging from 0 to 100, where 0 reflects poor effect and 100 reflects maximum positive effect.[23]

Other studies have investigated the effect of HDF on fatigue and have led to conflicting results. Ward et al. has shown that fatigue significantly improved during the study comparing HD with HDF, but increase did not depend on the therapy mode ($p = 0.083$).[24] Two studies reported that there was no evidence of a reduction in fatigue scores in patients switching from HD to HDF compared with those remaining on HD.[25,26] In the study of Kantartzi et al., the energy/fatigue component of the SF36 did not differ significantly between patients receiving HD and HDF.[27] Maruyama et al. have shown that the frequency and severity of fatigue, of both dialysis and nondialysis days, was similar in patients on HD and HDF.[28] Conversely, Karkar et al. showed an incremental benefit of 5.3 standardized mean difference in Fatigue score (SF36) when comparing HDF with HD.[29] Similarly, in the study of Knezevic et al., the energy/vitality domain of SF36 was significantly better in patients receiving HDF than in those on high flux or low flux hemodialysis.[29] Finally, the systematic review of Suwabe et al. demonstrated that online HDF was associated with a nonsignificant decrease of fatigue when compared with bicarbonate hemodialysis.[39]

The present study also shows that the characteristics of post-dialysis fatigue, intensity, duration, and frequency were similar in patients on HD and on HDF. This is also the first time that such results are found. Considering that intensity was defined as the magnitude of fatigue, duration as the length of time that fatigue lasted, and frequency as the number of times that fatigue happened, the definition of such characteristics gives a wide spectrum of the event post-dialysis fatigue in patients on chronic hemodialysis.

We also found that the length of recovery time after dialysis was similar in patients receiving HD or HDF. This result is in accordance with the study of Smith et al. who have recently demonstrated that there was no overall difference in recovery time after dialysis between HD and HDF treatments (medians for HDF vs. HD of 47.5 [IQR, 0–240] vs. 30 [IQR, 0–210] minutes, respectively; $p = 0.9$).[30] Similarly, Rayner et al. have found, in a large cohort, that the length of recovery time after dialysis was similar in patients on HDF and HD (OR, 1.08; 95% CI, 0.87–1.35).[31] Accordingly, the longitudinal study of Pecoits-Filho et al. have demonstrated that the difference in the change in recovery time after dialysis from baseline showed no significant distinctions between HD and HDF.[32]

The mechanisms underlying the lack of an association between HDF and lower post-dialysis fatigue prevalence remain unknown. Notably, in the present study, the intra-dialytic cytokine pattern and the inflammatory status were not studied.

Interestingly, we found that post-dialysis fatigue was significantly more frequent in female patients; it is the first time that such result is reported, and it seems that further studies are required to clarify the underlying mechanisms. However, there is evidence that the frequency of fatigue is higher in female patients also in other chronic diseases such as cancer[40–43] and multiple sclerosis.[44,45]

Our study has some limitations and some strengths. The strengths include multicentricity and a large sample size applied to a comparison of bicarbonate HD and online HDF in an important topic such as post-dialysis fatigue, so far not carefully considered in previous trials. The limitation is that, due to the cross-sectional nature of the study, any hypothesis of cause and effect cannot be made.

In conclusion, we show that the prevalence of post-dialysis fatigue and its characteristics as well as the length of recovery time after dialysis do not differ significantly between patients receiving HD and HDF. It is amenable that a prospective, randomized, longitudinal study will compare HD and HDF in terms of post-dialysis fatigue and recovery time after dialysis in the next future.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been involved in drafting the manuscript or revising it critically for important intellectual content; and given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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