Survival Benefit of Hemodiafiltration Compared With Prolonged High-flux Hemodialysis

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Introduction. Patients on dialysis have a high rate of death, mainly of cardiovascular cause. Nephrologists are actively looking for ways to improve patients' outcomes, and alternative dialysis strategies, such as long conventional hemodialysis and hemodiafiltration, are currently being investigated. The aim of this study was to compare anemia, nutrition, inflammation, mineral metabolism, and 3-year survival rates between patients treated with hemodiafiltration and prolonged high-flux hemodialysis (HFH).

Materials and Methods. A total of 58 dialysis patients were divided into 2 groups to undergo hemodiafiltration 3 times weekly, 12 hours in total per week, or prolonged duration of HFH (≥ 15 h/w). One-year biochemical parameters were collected retrospectively, together with 36 months patients' survival (prospectively).

Results. Patients in the HFH group had longer dialysis vintage; significantly higher levels of hemoglobin (despite less frequent use of erythropoietin-stimulating agents), serum albumin, serum calcium, and serum bicarbonate; and a lower intact parathyroid hormone level. Survival rates were comparable between the two groups. The Cox proportional hazard model showed that patients treated with longer HFH had a 32% relative risk reduction of mortality compared to patients treated with hemodiafiltration, but without statistical significance (hazard ratio, 0.68; 95% confidence interval, 0.21 to 2.20; adjusted for diabetes mellitus).

Conclusions. Longer duration of hemodialysis with high-flux membranes had beneficial effects on anemia indexes, mineral metabolism, nutrition parameters, and acidosis in comparison with hemodiafiltration. However, hemodiafiltration did not offer a 36-months survival benefit over prolonged HFH.

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INTRODUCTION

Traditional hemodialysis prescription consists of 3 sessions per week in duration of 4 hours and it is regarded as sufficient in most cases to reach adequate hemodialysis.[1] Adequate hemodialysis includes the optimal correction of anemia, immune competence, mineral-bone metabolism, nutritional disorders, general quality of life, and improved morbidity and mortality.[2] During the 1960s, chronic hemodialysis usually included 3 sessions per week in duration of 8 to 12 hours.[3,4] Advanced dialysis membranes and techniques led to reduction in the length of dialysis to 4 hours since the clinical outcome of such prescription was considered acceptable.[5] However, despite the significant scientific and technological progress in dialysis treatment that has been made over the last few decades, these patients still maintain a high rate of morbidity and mortality, mainly of cardiovascular cause, compared with the general population. Therefore, nephrologists are actively looking how to improve patients' outcomes.[6] At present, a number of alternative dialysis strategies, such as long conventional hemodialysis and hemodiafiltration, are currently being investigated.[6]

During hemodiafiltration, the clearance of uremic toxins of small and middle molecular mass is additionally increased with convective transport compared to high-flux hemodialysis.[7] In addition, some epidemiological studies as well as meta-analyses suggest survival benefit in patients treated with hemodiafiltration.[8,9]

In the past few years, several studies have shown that increased dialysis length can lead to better correction of anemia parameters, along with the reduction in the frequency of administration and dose of erythropoietin-stimulating agents (ESA).[10,11] At the same time, the increased dialysis length was associated with better control of hyperphosphatemia and prevention of secondary hyperparathyroidism, along with reduced frequency of administration of phosphate binders and metabolite of vitamin D.[12,13] Furthermore, there are several reports about the positive effects of prolonged hemodialysis sessions on nutritional parameters and higher survival rate.[6,10,14-17] Studies were mainly conducted in developed countries where survival of patients could be influenced by additional factors of different standards of care as compared with developing countries.

The aim of study was to compare the parameters of anemia, nutrition, inflammation, mineral metabolism, and 3-year survival rate between patients treated with hemodiafiltration and prolonged high-flux hemodialysis (HFH). There are numerous studies that compare standard conventional hemodialysis and hemodiafiltration, but to our knowledge, this is the first study that compares hemodiafiltration and prolonged standard bicarbonate HFH.

MATERIALS AND METHODS

This study included a total of 58 patients selected out of 206 who satisfied the inclusion criteria of the study and who were treated with chronic hemodialysis for more than 6 months at the Department of Nephrology and Disorders of Metabolism with Dialysis. The study protocol was approved by the University Hospital Ethics Board, and all of the patients signed an inform consent form after being provided with detailed information about the study protocol.

The patients were classified and analyzed according to the hemodialysis modality and the total duration of dialysis treatment per week into 2 groups: the patients treated with hemodiafiltration in total duration of 12 h/wk and the patients treated with prolonged duration of hemodialysis with HFH (the total duration of dialysis treatment, ≥ 15 h/wk). The target convection volume in the HFH group was above 15 L and patients received 17.0 ± 2.5 L on average. The exclusion criteria were treatment with low-flux membranes or with high-flux membranes in duration less than 15 h/wk. The primary outcome of the study was 36-month patients' survival. Laboratory parameters were analyzed retrospectively for the period of 1 year while the survival of the patients was followed-up prospectively for the period of 3 years.

The samples for laboratory analyses were taken at the beginning of dialysis procedure after a weekend pause quarterly, and the following laboratory serum parameters were analyzed: total proteins, albumin, bicarbonate, C-reactive protein, hemoglobin, ferritin, calcium, phosphorus, total cholesterol, high-density lipoprotein cholesterol, and triglycerides, which were measured by standard laboratory techniques. The average of analysis was calculated for the period of 1 year, except the values for parathyroid hormone, which was checked at least twice a year using chemiluminescent assay (Diagnostic Product Corporation, USA).

The patients' data taken from medical records were age, sex, duration of dialysis (expressed in months), presence of diabetes mellitus and hypertension, cardiovascular diseases until the beginning of the study, intake of vitamin D metabolites (calcitriol) and phosphate binders (all patients received calcium-based phosphate binder, calcium carbonate), cumulative dose of calcium carbonate and vitamin D metabolites during the past year, the use of statins, and weekly dose of ESA.

Body mass index was calculated according to the patients' weight and height.[18] Erythropoietin resistance index was expressed as a quotient of average weekly ESA dose and body mass of the patient divided by average hemoglobin value. The adequacy of dialysis was expressed using KT/V for urea in accordance with Daugirdas formula.[19]

Cardiovascular morbidity score was calculated for each patient and on the basis of previous medical dialysis data file, by giving 1 point for each of the following diagnosis: cardiomyopathy, ischemic heart disease, peripheral vascular disease, and stroke.

Statistical calculations were performed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA). Data were expressed as percentage for discrete variables and mean values for continuous variables. Statistical analyses included exploratory analysis method (descriptive and analytic statistics). The independent sample *t* test was used to compare the variables with normal distribution on different groups. In cases where variables did not have normal distribution, the Mann-Whitney test was used. The Cox proportional hazard model was used to establish the impact of hemodialysis modality and treatment time duration on the patients' mortality. Survival analysis was performed using the Kaplan-Meier method, while the statistical significance was tested using the log-rank test. For all comparisons, a *P* value less than .05 was considered significant.

RESULTS

The Table summarizes characteristics of the patients and parameters of anemia, nutrition, lipids, inflammation, cardiovascular comorbidity score, and treatment details. Patients in the HFH

Demographic and Clinical Characteristics of Patients Treated With Hemodiafilration and High-flux Hemodialysis*

Characteristic	Hemodiafiltration Group (n = 26)	High-flux Hemodialysis (n = 32)	*P*
Male sex, %	46.2	28.1	> .05
Mean age, y	57.4 ± 10.3	57.1 ± 9.6	> .05
Type of vascular access, %			
Arteriovenous fistula	92.3	90.6	
Arteriovenous graft	7.7	3.1	
Catheter	0	6.3	> .05
Statin use, %	76.9	75.0	> .05
Hypertension, %	88.5	93.8	> .05
Diabetes mellitus, %	3.1	23.1	< .05
Cardiovascular comorbidity score	1.19 ± 1.06	0.84 ± 1.16	> .05
Dialysis vintage, mo	117.9 ± 39.1	171.1 ± 90.8	.005
KT/V	1.49 ± 0.28	1.50 ± 0.40	> .05
Hemoglobin, g/dL	10.6 ± 0.7	11.6 ± 1.5	.002
Serum ferritin, µmol/L	412 ± 237	281 ± 381	> .05
Erythropoietin-stimulating agents use, %	80.8	50.0	.03
Erythropoietin-stimulating agent weekly dose, IU	7071 ± 5820	5737 ± 4150	> .05
Erythropoietin resistance index, U/kg/wk	10.4 ± 9.9	7.6 ± 5.5	> .05
Body mass index, kg/m^2	23.7 ± 4.8	25.7 ± 4.6	> .05
Serum albumin, g/L	37.9 ± 3.2	41.1 ± 2.5	< .001
Total cholesterol, mmol/L	4.7 ± 1.0	4.8 ± 1.3	> .05
Low-density lipoprotein cholesterol, mmol/L	2.7 ± 0.7	2.7 ± 1.0	> .05
High-density lipoprotein cholesterol, mmol/L	1.1 ± 0.3	1.1 ± 0.3	> .05
Triglycerides, mmol/L	2.3 ± 2.3	2.2 ± 1.4	> .05
C-reactive protein, mg/L	9.0 ± 9.6	8.4 ± 7.9	> .05
Intact parathyroid hormone, pg/mL	451.9 ± 402.0	287.5 ± 351.0	.04
Serum bicarbonate, mg/dL	17.2 ± 3.8	21.7 ± 2.3	< .001
Serum calcium, mmol/L	2.31 ± 0.12	2.41 ± 0.18	.03
Serum phosphorus, mmol/L	1.65 ± 0.41	1.49 ± 0.40	> .05
Phosphate binders use, %	92.3	75.0	> .05
Vitamin D use, %	53.8	43.8	> .05
Yearly cumulative calcium carbonate dose, g	1238 ± 664	1385 ± 724	> .05
Yearly cumulative dose of vitamin D metabolites, U	400 ± 398	454 ± 314	> .05

group had longer dialysis vintage compared with patients in the hemodiafiltration group. They also had better acid base status and were less likely to have DM. There was no difference among the groups regarding the presence of hypertension, type of vascular access, age, sex distribution, dialysis adequacy, and frequency of statin use. The patients in the HFH group had a lower average value of cardiovascular comorbidity score (0.84 ± 1.06) compared to the patients in the hemodiafiltration group (1.19 ± 1.06), but the difference did not reach statistical significance.

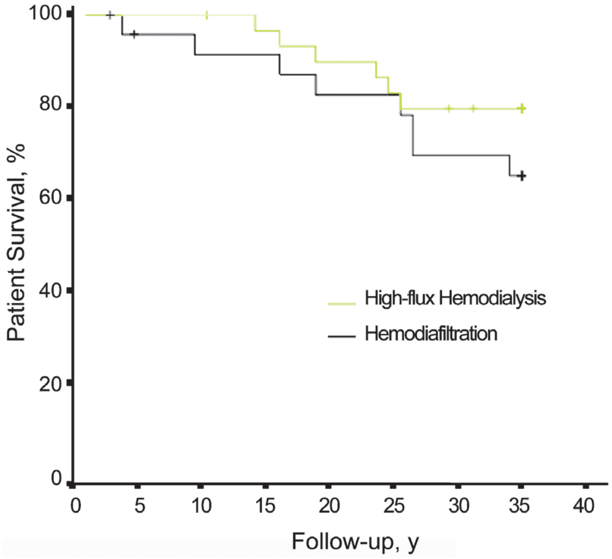
The patients in the HFH group had significantly higher values of hemoglobin, despite the less frequent use of ESA. They also had a lower erythropoietin resistance index and mean weekly ESA dose, but without statistical significance, while they had significantly higher values of serum albumins than those on hemodiafiltration group. The values of body mass index, lipids, ferritin, and C-reactive protein did not differ significantly between the groups.

The patients in the HFH group had lower average values of intact parathyroid hormone, despite the less frequent use of phosphate binders and vitamin D metabolites (statistical significance was not reached). There were no differences between the groups in average phosphorus levels, while the average value of calcium was significantly higher in the patients of the HFH group. There was no difference in the cumulative yearly dose of calcium carbonate and the metabolite of vitamin D in the patients receiving such therapy.

At the end of a 36-month follow-up period, 14 patients died, 8 from the hemodiafiltration group and 6 from the HFH group. The Kaplan-Meier survival analysis showed comparable survival rates between the two groups (Figure). The Cox proportional hazards model showed that patients treated with longer HFH treatment had a 32% relative risk reduction of mortality compared to patients treated with hemodiafiltration, but without statistical significance (hazard ratio, 0.68; 95% confidence interval, 0.213 to 2.199; adjusted for diabetes mellitus).

DISCUSSION

In the present study, patients treated with HFH for 15 hours and more had significantly better correction of plasma bicarbonate, hemoglobin, albumin, and mineral metabolism indexes as compared with patients treated by hemodiafiltration. Our data are in agreement with authors who noticed better control of acidosis in patients treated with longer dialysis duration regardless of dialysis modality.[10,20] However, the others did not spot this difference.[21]



Kaplan-Meier survival curves of patients treated with hemodiafiltration and prolonged high-flux hemodialysis (log-rank test, $P > .05$).

Although without statistical significance, favorable effect of prolonged HFH compared to hemodiafiltration was found for some parameters of anemia since the patients from this treatment group had higher values of hemoglobin with less frequent use of ESA. Also, there was a trend towards a lower average dose of ESA and lower erythropoietin resistance index in patients with prolonged hemodialysis, but the difference between the groups did not reach statistical significance, probably due to relatively small number of patients. Some observational studies which compared hemodiafiltration and conventional hemodialysis for similar treatment time found certain benefits of hemodiafiltration to anemia indexes.[22] However, larger and more recent studies did not confirm those benefits.[23-25] Ok and colleagues reported that after a year of treatment, the patients who had 8 hours of treatment 3 times per week experienced the increase of hemoglobin value, and at the same time, there was a decrease in frequency of ESAs use from 55% to 24.7% with simultaneous reduction of weekly ESAs dose.[10] The reason for favorable effect of longer dialysis on anemia in the setting of similar KT/V is probably multifactorial. It is possible that the clearance of middle molecules, including the inhibitors of erythropoiesis is more efficient with longer hemodialysis than with hemodiafiltration.[20]

Numerous studies, including this one, have indicated the importance of nutritional status for survival of dialysis patients. Body mass index values were not significantly different between our two groups. Also, the patients with longer duration of hemodialysis procedure were found to have significantly higher values of serum albumin. These findings suggest the better nutritional status of these patients, which is in accordance with data reported by other authors who focused only on the treatment time regardless the modality.[10,14,15,26,27] Neither did some recent prospective studies find a difference in the nutritional status between the patients treated with HFH and hemodiafiltration in patients treated with the same duration of sessions.[21,28] This suggests that the nutritional status hardly depends on the type of membrane and dialysis technique. Since C-reactive protein levels did not differ between our two groups, better correction of anemia and nutritional status is unlikely the result of apparent or silent inflammation. Better correction of acidosis in patients in the HFH group may have contributed to better appetite and at the same time to better nutritional parameters. This study did not monitor leptin values, but there is a possibility that prolonging the time of dialysis increases the elimination of leptin and consequently increases the appetite and parameters of nutrition.

This study confirmed the relationship between parameters of mineral metabolism and duration of dialysis treatment. Lower values of intact parathyroid hormone were recorded in the patients from the HFH group (287 pg/mL versus 451 pg/mL) although the patients from the HFH group used vitamin D metabolites less frequently (44% versus 54%). It is important to mention that number of patients who had their intact parathyroid hormone level corresponding adynamic bone disease did not differ between the groups (29% in the hemodiafiltration group versus 38% in the HFH group). The patients from the hemodiafiltration group had a lower calcium value, which is in accordance with intact parathyroid values. There was no significant difference among the groups in phosphorus values even though the patients from the HFH group used phosphate binders less frequently (75% versus 92%). There was no difference between the groups in cumulative yearly dose of vitamin D metabolites and yearly dose of calcium carbonate. Reduced frequency of phosphate binder prescription following the prolonged dialysis procedure as well as an increase in serum calcium was also observed by other authors.[10] Lower frequency of secondary hyperparathyroidism was recorded in Tassin group of patients as compared to other parts of France and Europe with less frequent use of phosphate binders.[6] In the CONTRAST study, a decrease in intact parathyroid values was not seen after switching from low-flux hemodialysis to hemodiafiltration,[29] suggesting that hemodiafiltration treatment did not lead to a better intact parathyroid control. In addition, the same study did not reveal a reduction in frequency and dose of phosphate binders after switching to hemodiafiltration.

The patients from the HFH group did not have better 3-year survival compared to the patients in the hemodiafiltration group. But prolonged HFH was related to a 32% relative risk reduction of mortality compared to patients treated with hemodiafiltration, but without statistical significance. Some observational studies reported better survival of the patients treated with hemodiafiltration compared to the patients treated with HFH.[21] However, several randomized controlled studies as well as meta-analyses which compared survival of the patients treated with hemodiafiltration and HFH (for the same treatment time) did not find a difference in patients' survival,[30-34] except for the ESHOL study and post hoc analysis in ''Turkish study'' when high substitution volumes during hemodiafiltration were used.[31,33] The very recent publication by Peters and coworkers[35] summarized the data from 4 trials, the CONTRAST, French Hemodiafiltration Study, ESHOL Study, and Turkish Hemodiafiltration Study, to summarize the outcome of 2792 patients randomized to either hemodiafiltration or standard hemodialysis. According to this analysis, online hemodiafiltration reduced the risk of all-cause mortality by 14% and cardiovascular mortality by 23%. The largest survival benefit was for patients receiving the highest delivered convection volume (> 23 L/1.73 m^2 body surface area per session), with a multivariable-adjusted hazard ratio of 0.78 for all-cause mortality and 0.69 for cardiovascular disease mortality.[35] The amount of convective volume during hemodiafiltration in our patients was 17.0 ± 2.5 L/1.73 m^2 per session, average with a good KT/V. Still, we believe that a larger volume of substitution fluid (up to 25 L) could positively affect patients' outcome and it could be one of the reasons we had these results. On the other hand, numerous studies suggest lower mortality of patients whose hemodialysis procedures are longer than traditional 4-hour dialysis session (which is similar to our results).[10,17,26]

This study has its limitations. Although the aim of the study was to examine the impact of treatment modality and duration of hemodialysis per week on adequacy parameters and 3-year survival rate, the groups of patients were not homogenous by dialysis vintage and presence of diabetes mellitus. Also, this study was done with prevalent patients and current findings should be supplemented with data from incident patients. In addition, many of the findings, such as better control of hemoglobin level and serum bicarbonate in the HFH group could be achieved only by prolonged dialysis regardless of membrane characteristic, and this possibility cannot be clarified by the current study design. Taken together, results presented in this study should be taken with caution and need to be confirmed by further investigations on larger number of patients.

CONCLUSIONS

Longer duration of hemodialysis with high-flux membranes (≥ 15 hours) had beneficial effects on anemia indexes, nutrition parameters, acidosis, and probably mineral metabolism in comparison with hemodiafiltration. Hemodiafiltration did not offer survival benefit over longer HFH; albeit without statistical significance patients treated with longer HFH had a lower relative risk of mortality than patients treated with hemodiafiltration during the 3 years of follow-up period. Longer follow-up is necessary in order to establish an advantage in survival among individual dialysis methods.

CONFLICT OF INTEREST

None declared.

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