Survival of Patients Treated with Online Hemodiafiltration Compared to Conventional Hemodialysis

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ABSTRACT

Accumulating data from observational studies showed that online hemodiafiltration (OLHDF) might improve survival in chronic hemodialysis (HD) patients. According to this data, the aim of our study was to investigate whether there was a difference in survival of patients treated with OLHDF compared to standard, conventional HD. We included 85 prevalent patients with end-stage renal disease (ESRD) treated with HD as a method of renal replacement therapy (RRT) for more than three months. Patients were previously treated with HD and divided into two groups: in 42 patients new treatment with OLHDF was introduced, and 43 patients were treated with HD. Both groups were followed over a period of 36 months. The study showed significantly better survival of patients treated with OLHDF, compared to the survival of patients treated with HD in the whole study population, as well as in the subgroups of diabetics, of patients who were on RRT with HD for more than five years and of the patients who were older than 65 years. In the nondiabetics, patients who were on RRT for less than five years and in the patients who were younger than 65 years, survival results in the OLHDF group were not significantly better compared to those in the HD group. As in our study, there are accumulating data from observational studies that HDF may improve survival in chronic HD patients, but new, prospective randomized trials are needed to support evidence about this hypothesis.

Key words: hemodiafiltration, hemodialysis, mortality, membranes, survival

Introduction

Significant increase in the incidence and prevalence of chronic kidney disease (CKD) has been observed worldwide. Epidemiological studies that include most industrialized countries and some developing countries have shown that approximately every tenth adult in the world or about 10% of the population in the developed countries has CKD.

Therefore, today, worldwide more than one million patients are treated with hemodialysis (HD) as a method of choice of renal replacement therapy (RRT) in the end stage renal disease (ESRD). Due to the rapid development of dialysis technology over the last four decades, RRT with dialysis has become a routine procedure, although, morbidity and mortality in patients treated with dialysis are still very high1,2. Cardiovascular diseases are the leading cause of morbidity and mortality of patients with ESRD, to a greater extent than in the general population. In fact, about 50% of deaths in these patients are related to cardiovascular causes3,4. ESRD patients are exposed to numerous cardiovascular risk factors5. Some of these factors are related to the primary disease that led to the failure of renal function, and to associated diseases and conditions, and some to undesirable effects and complications of dialysis procedure6. Cardiovascular risk factors that patients in ESRD are exposed to, can be divided into two groups. These are »traditional« general risk factors, such as older age, male gender, diabetes, hypertension, dyslipidemia, and »nontraditional,« »uremic«, car-
diovascular risk factors, whose importance is growing with renal function deterioration. Important ‘uremic’ cardiovascular risk factors are malnutrition, inflammation, atherosclerosis, anemia, increased extracellular volume, thrombogenic factors, low delivered dose of dialysis, type of dialysis membrane, type of dialysis procedure, hyperphosphatemia, amyloidosis due to deposition of β2-microglobulin, etc. Association of separate cardiovascular risk factors increases the incidence of cardiovascular disease significantly. Inflammation and oxidative stress that patients receiving hemodialysis treatment are exposed to, to a significant extent, are of particular importance. Inflammation and oxidative stress lead to endothelial dysfunction and accelerated development of atherosclerosis. One way to reduce hemodialysis-induced inflammation and oxidative stress is the use of OLHDF. In contrast to diffusive dialysis transport, which mainly remove toxins of small molecular weight, in hemodiafiltration, diffusive and convective transport are combined, providing an optimal removal of both, small and large, uremic toxic molecules. Clinical studies have suggested that use of this method leads to reduction of cardiovascular morbidity and mortality in these patients. According to these observations, the aim of our study was to evaluate whether there is a difference in survival of patients treated with OLHDF compared to survival of patients treated with standard, conventional HD and to which extent.

**Patients and Methods**

The study included 85 patients on chronic program of RRT. The follow-up period was 36 months. Three dialysis centers have agreed to provide the required number of patients. All patients were older than 18 years, and signed the informed consent approved by the local Ethics committee. The study was conducted in keeping with good clinical practice guidelines. The patients with ESRD were on regular HD for at least three months. Of the 85 patients studied, 43 were treated with low-flux HD but in 42 patients new treatment with OLHDF was introduced, when became available, randomly. The follow-up in the both patients groups was 36 months. The intended HD treatment duration for both modality arms of the trial was 240 min with a blood flow rate between 250 and 400 mL/min, as registered in a single hemodiafiltration treatments. Patients with a blood flow lower than 250 mL/min, registered in the more than 30% treatments 3 months before enrollment were not included in the study. Most patients has an AV fistula as a vascular access (88% in OLHDF group and 86% in HD group, respectively) and other patients has a catheter (12% vs 14%, respectively). The dialysate flow rate was kept at 500 mL/min in both groups. The same high-flux dialyser (Polsulfone-based Helixone Membrane, Fresenius Medical Care, Bad Homburg, Germany) was used during the entire study period. Dialysate composition was the same in >90% of subjects in both arms of the study (Na 138 mmol/L, K 2.0 mmol/L, Ca 1.25 mmol/L, Mg 0.5 mmol/L, Cl 109 mmol/L, HCO3 32 mmol/L, acetate 3 mmol/L, glucose 5.5 mmol/L). Sodium modelling was not applied. Low molecular weight heparin was used for anticoagulation. Dialysate reuse was not permitted. Standard dialysate was utilized in the HD group. OL-HDF procedure was performed in the postfiltration mode under strict safety operational procedures. Fresenius 5008S dialysis machines, incorporating the ONLINEplus (Fresenius Medical Care, Bad Homburg, Germany) system were used. This system consists of two ultrafilters (DIASAFEplus); the first one is placed after the proportioning system and the second is positioned before the substitution port. Ultrafilters in-stalled on the haemodiafiltration (HDF) machine were replaced after 100 treatments or 12 weeks of use, whichever came first. Dialysate in the HD group and infusate in the OL-HDF group were regularly assessed for colony-forming units and endotoxin levels before change of ultrafilters. In the OL-HDF mode, the filtration rates were adjusted to be between 25 and 30% of the achieved blood flow rate and substitution volume was targeted to be above 19 L per session. The electrolyte composition of the infusate was the same as the composition of the dialysis fluid. During the study period, we analyzed the overall survival of patients treated with OLHDF compared to survival of patients treated with conventional HD. Also, we compared survival of patients divided into subgroups with respect to four important criteria, such as age, vintage of RRT with HD, presence of diabetes and whether they were or they were not on kidney waiting list for transplantation.

**Statistics**

Statistical analysis of data was performed using descriptive statistics (mean and standard deviation). Categorical variables were tested by Fisher Exact test. Testing the importance of the difference of two independent groups was performed using t-test. The difference in survival of patients was analyzed with Kaplan-Meyers’s method of mortality risk. P-value <0.05 was considered to be statistically significant. Statistical analysis was made using licensed MedCalc statistical software package, version 11.5 (MedCalc, Mariakerke, Belgium).

**Results**

Out of 85 patients, there were 24 male (57.1%) and 18 female (42.9%) in the OLHDF group, and 26 male (60.5%) and 17 female (39.5%) in the HD group. There were no statistically significant difference between the two groups related to gender, hemodialysis treatment parameters, hemoglobin level, erythropoiesis stimulating agents use, blood pressure and concomitant medication use (Table 1). The average age of patients was 58.45±11.04 years in the OLHDF group, and 62.02±12.32 years in the HD group. There was no statistically significant difference in age between the groups (p=0.1634).

Furthermore, there was no statistically significant difference in the vintage of dialysis treatment between the two groups. The average time of RRT with hemo-
Dialysis was 99.69 ± 105.78 months in the OLHDF group, and 84.90 ± 78.31 months in the HD group (p = 0.4654).

In both groups of patients, primary renal disease was chronic glomerulonephritis (in 35.7% of patients in the OLHDF group and 30.2% in the HD group). Diabetic nephropathy followed in frequency in both groups (11.9% in OLHDF and 11.6% in HD group). In one of the patients in OLHDF group and in four in the HD group primary renal disease was unknown (Table 2).

In Kaplan-Mayer survival analysis patients in the OLHDF group had significantly better survival compared to those in the HD group (p = 0.0172). Specifically, in the OLHDF group five patients died, while in the group of patients treated with HD there were 14 deaths (Figure 1).

When patients were divided in subgroups according to four important criteria, such as duration of dialysis, age, status on the waiting list for kidney transplantation and presence or absence of diabetes, significantly better survival of patients treated with OLHDF in the diabetic group (p = 0.0449) was obtained, as well as in the group of patients who were not on the waiting list for kidney transplantation (p = 0.0311), in the group of patients who were treated with hemodialysis for more than five years (p = 0.0097) and in the group of patients older than 65 years (p = 0.0200). In the nondiabetic group, in patients who were treated with dialysis for less than five years and in patients younger than 65 years, we have found better survival in the OLHDF group but the difference was not statistically significant.
In patients on the waiting list for kidney transplantation survival rates were better in the group treated with standard, conventional HD, but the difference was not statistically significant (p=0.3417). Overall survival rates and survival rates of patients by subgroups are shown in Table 3.

### Discussion

The aim of our study was to investigate whether OLHFD had favorable effect on the outcome of patients compared to conventional low-flux HD. We presented favorable effect of OLHDF in reducing the overall risk of mortality in the whole study population, as well as in certain subgroups of patients, such as diabetics, patients older than 65 years, patients who were on chronic RRT program for more than five years and HD patients who were not on the waiting list for kidney transplantation. Thus, we have shown the beneficial effects of OLHDF in the study population as a whole and in vulnerable groups of patients.

Two large controlled, randomized studies (HEMO and MPO) failed to demonstrate a beneficial effect of high-flux membranes on overall survival outcomes. They examined the effect of high-flux membranes compared to low-flux, but not the impact of convective methods (HDF and HF) compared to standard low-flux hemodialysis.

HEMO study is a large, multi-center, randomized controlled trial conducted in the U.S., which included 1846 prevalent patients who were on chronic RRT program with HD for more than three months. Patients who were on chronic HD program for less than three months were excluded from the study, as well as those whose total level of serum albumin was less than 2.6 g/dL, and patients with very large body weight, if it was not possible to achieve the target Kt/V index of 1.3. Primary analyses showed no statistically significant differences in survival of patients on high-flux compared to low-flux membranes, while secondary analyses showed a statistically significant beneficial effect of high-flux membranes on the outcome of patients who were on HD for more than 3.7 years.

MPO is also a large multi-center, controlled, randomized study conducted in Europe, which included 738 HD incident patients. It also failed to prove beneficial effects of high-flux membranes on overall survival outcomes, but in the group of patients with serum albumin below 4 g/dl, the results were significantly better in patients on high-flux membranes, as well as in patients with diabetes in secondary analysis.

In a retrospective study, Vilar and colleagues compared the effects of high-flux HD and OLHDF on clinical outcomes, including patient survival. The study included 856 patients who were dialyzed in their center over a period of 18 years. Patients were divided into two groups depending on whether they were predominantly treated with high-flux HD or HDF. Survival rates were statistically significantly better in the predominantly HDF group.

Cannaud and colleagues conducted the study as part of the DOPPS study (Dialysis Outcomes and Practice Patterns Study). This prospective, longitudinal, observational study included 2165 patients from five European countries. Results showed 35% lower risk of mortality in the group of patients treated with high-efficiency HDF compared to patients treated with low-flux HD.

The results of this study are confirmed by Jirka and his associates, also in an observational, multi-center study, which included 2546 patients from 56 centers in four major European countries. They showed a 42.7% reduction of mortality risk in the group of patients treated with HDF compared to patients treated with low-flux HD. After adjusting for age, sex, comorbidities and time of RRT, the difference remained statistically significant (35.3%).

RISCAVID study is another observational study that showed a favorable effect of HDF on reducing mortality risk. It is a prospective study that included 757 patients who were monitored over a period of 30 months. The results showed a favorable effect of HDF on patients’ survival compared to low-flux hemodialysis.

### Table 3

<table>
<thead>
<tr>
<th>Method of RRT</th>
<th>All patients</th>
<th>Less than 5 years on hemodialysis</th>
<th>More than 5 years on hemodialysis</th>
<th>Older than 65 years</th>
<th>Younger than 65 years</th>
<th>Patients on kidney transplantation list</th>
<th>Patients not on kidney transplantation list</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>43 42 20 22 23 20 21 10</td>
<td>22 32 7 16</td>
<td>36 26 5 5 38 37</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Number of lethal outcome</td>
<td>14 5 5 4 9 1 9 0</td>
<td>5 5 0 2</td>
<td>14 4 3 1 11 4</td>
<td></td>
<td></td>
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</tbody>
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* P<0.05, ** P<0.01, RRT – renal replacement therapy, OLHDF – online hemodiafiltration, HD – conventional hemodialysis
CONTRAST study (The Dutch Convective Transport Study) is a multi-center, randomized, controlled study that included 772 patients. The aim of this study was to investigate the effect of treatment modalities (OLHDF and low-flux HD) on overall mortality from any cause, and the morbidity and mortality due to cardiovascular causes. The results failed to demonstrate a significant difference in the survival of patients on OLHDF compared to those on low-flux HD, but subgroup analyses showed significantly better survival in patients on OLHDF who have reached substitution volumes greater than 20 liters per treatment. Main limitation of our study is a small number of patients, but still identifies vulnerable subgroups of patients, potentially with the highest mortality, especially cardiovascular. Therefore, our findings can be very useful for further investigations.

**Conclusion**

Although these studies, including our own, show the beneficial effect of hemodiafiltration on improving clinical outcomes and survival in chronic HD patients, there is a need for stronger evidence from a large randomized controlled trials to confirm this hypothesis.

**REFERENCES**


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**PREŽIVLJENJE BOLESNIKA LIJEČENIH METODOM »ONLINE« HEMODIJAFILTRACIJE U USPOREDBI S KONVENCIONALOM HEMODIJALIZOM**

**S A Ž E T A K**

Dostupni podaci iz opservacijskih studija pokazuju da primjena »online« hemodijafiltracije (OLHDF) može poboljšati preživljavanje bolesnika liječenih kroničnom hemodializom (HD). Sukladno tome, cilj našeg istraživanja bio je ispitati postoji li razlika u preživljavanju pacijenata liječenih OLHDF odnosu na standardnu, konvencionalnu HD. U istraživanje je uključeno 85 bolesnika u 5. stadiju kronične bubrežne bolesti (KBB) koji su liječeni HD kao metodom nadomjesanja bubrežne funkcije (NBF) tijekom više od tri mjeseca. Svi pacijenti su prethodno liječeni sa HD te su podijeljeni u dvije skupine: u 42 bolesnika primijenjen je novi postupak (OLHDF), dok je preostalih 43 pacijenta i dalje liječeno konvencionalnom HD. Obje skupine su praćene tijekom 36 mjeseci. Rezultati su pokazali značajno bolje preživljavanje pacijenata liječenih sa OLHDF, u odnosu na pacijente liječene sa HD u cijeloj promatranoj populaciji, kao i u podgrupama dijabetičara, pacijenata koji su bili na NBF dulje od pet godina i u pacijenata koji su bili stariji od 65 godina. U nedijabetičara, pacijenata koji su bili na NBF manje od pet godina te u bolesnika koji su bili mladi od 65 godina, nije zabilježeno bolje preživljavanje u OLHDF grupi u odnosu na pacijente u HD grupi. Kao što je prikazano u ovom istraživanju, postoje podaci iz opservacijskih studija da HDF može poboljšati preživljavanje u bolesnika na kroničnoj hemodializi, posebno u nekim podgrupama pacijenata, ali su potrebna prospektivna istraživanja, na većem broju bolesnika za potvrdu te hipoteze.