

Research Article

Clinical and Biological Benefits of Daily Online Hemodiafiltration

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Abstract

Introduction: Daily Online Hemodiafiltration (D-OL-HDF), by combining OL-HDF and daily hemodialysis, is an interesting alternative modality for ESKD patients. First results were reported by Fischbach et al., on children and by Maduell et al., on adult's patients in 2003: excellent clinical tolerance and better dialysis adequacy allowing a better quality of life, an improvement in nutritional status, a better control of anemia and blood pressure and a reduction of left ventricular mass were reported. However, there is no data regarding this technique since 2003. We studied here retrospectively ten patients treated with D-OL-HDF and followed them during twelve-months to evaluate the benefits of this modality.

Material and Methods: All 10 patients, treated with D-OL-HDF between 2011 and 2015 in our centre, were included in this study. Data were collected monthly after changing three times a week OL-HDF to D-OL-HDF (six or five times a week, 2 to 2.5 hours by session respectively): dialysis adequacy, hemodynamic and cardiovascular parameters, bone's parameters and nutritional status have been evaluated.

Results and Discussion: As expected, the Interdialytic Weight Gain (IDWG) was significantly lower as well as the value of Brain Natriuretic Peptid (BNP) and, in meanwhile, a gain in Left Ventricular Ejection Fraction (LVEF) after twelve months was obtained. We observed also a significant increase in haemoglobin value and in serum albuminemia whereas other parameters remained stable. Moreover, phosphate binders and oral calcium supplementation were reduced during the follow-up.

Discussion: These benefits are consistent with those presented by Maduell et al: D-OL-HDF seems to be an excellent technique and should be considered as an alternative treatment to three times a week conventional treatment.

ABBREVIATIONS

β2m: Beta-2-microglobulin; BNP: Brain Natriuretic Peptid; BMI: Body Mass Index; BP: Blood Pressure; ESRD: End Stage Renal Disease; FAT: Fat Adipose Tissue; FHN: Frequent Hemodialysis Network; FTI: Fat Tissue Index; HDF: Hemodiafiltration; IDWG: Interdialytic Weight Gain; LVEF: Left Ventricular Ejection Fraction; OL-HDF: Online-Hemodiafiltration; SD: Standard Deviation D-OL-HDF: Daily-Online-Hemodiafiltration.

INTRODUCTION

For forty years, dialysis techniques have been dramatically improved. Latest publications have described the superiority in terms of morbidity and mortality of the Online-Hemodiafiltration (OL-HDF) technique [1], as well as the daily and long hemodialysis techniques [2]. However, there are very few studies regarding

the short daily OL-HDF (D-OL-HDF) technique.

By combining diffusive and convective solute transfer through high flux dialyzer membrane, OL-HDF is considered the most efficient technique for both small and large uremic toxins elimination [3]. Uremic toxins are shown to have a pathogenic role in the occurrence of long-term complications affecting hemodialysed patients [4,5]. OL-HDF improves clinical and biochemical parameters as well as patients' quality of life, when compared with conventional hemodialysis [6]. Although, the primary analyses of three large randomized controlled trials showed inconclusive results due to a non-significant difference in all-cause mortality or cardiovascular events between OL-HDF and HD [7-9]. Post-hoc analysis of these studies, as well as the meta-analysis conducted by Mostovaya et al, suggests a positive effect of post-dilution OL-HDF modality over standard hemodialysis in

reducing cardiovascular and all-cause mortality [1,3]. Moreover, the relationship between a convective volume over 23 L/session and a decrease in mortality rate was demonstrated in these post-hoc analysis [3,9].

Daily hemodialysis compared to three-weekly hemodialysis, increases the nutritional status, and decreases the over-hydration allowing a better tolerance of ultrafiltration rate and, subsequently, a better blood pressure control [10]. Moreover, Frequent Hemodialysis Network (FHN) randomized trials showed that daily dialysis improves mental and physical health and is associated with reduction in left ventricular mass [11-13]. A recent study conducted by Chertow et al. showed that frequent hemodialysis reduces long-term mortality of selected patients with End Stage Renal Disease (ESRD) [2].

Daily OL-HDF, by combining OL-HDF and daily hemodialysis is an interesting alternative modality, firstly described by Fischbach et al in children [14]. These authors reported good benefits of this technique such as: less tiredness, better appetite, increase in Body Mass Index (BMI) and catch up growth, optimal blood pressure control and less interdialytic weight gain associated to a reduction of left ventricular hypertrophy [15].

Recently, Maduell et al., in a prospective study of eight patients followed for six months, described a better control of anemia, nutrition, blood pressure, as well as a reduction of phosphate binders and a noticeable regression of left ventricular hypertrophy in daily OL-HDF than with standard Hemodialysis [10]. At this time, this study was the only one reporting this technique for adult patients.

We studied here retrospectively ten patients treated with D-OL-HDF and followed them for twelve-month to evaluate and confirm the benefits of this modality.

MATERIALS AND METHODS

The study was conducted retrospectively over a period of 12 months between 2011 and 2015 in our centre, starting at the beginning of daily OL-HDF.

All of the patients treated with D-OL-HDF in our centre were included (6 men and 4 women). They all gave their informed consent to participate in the study.

The median age was 55.5 ± 18 (range 29 to 86 years), and the median dialysis vintage was 1.6 years (range: 0.08 to 26.7 years). The underlying renal diseases were glomerular nephropathy (n=5), diabetic nephropathy (n=1), polycystic kidney disease (n=1), others (n=3). The baseline residual renal function was lower than 4 mL/min.

Eight patients were included in daily OL-HDF technique while they were already treated at least 3 months with three-weekly OL-HDF. The two others were immediately treated with D-OL-HDF at the initiation of hemodialysis treatment.

Daily-OL-HDF modality was indicated either for medical intolerance to standard hemodialysis (n=2) or for personal convenience (n=8).

All patients were hemodialysed with a native arterio-venous fistula allowing a bipuncture and a blood flow ≥ 300 mL/min.

The session length of daily-OL-HDF was 2 hours six times a week (n=6) or 2.5 hours 5 times a week (n=4). In all cases, the weekly treatment duration was 12 hours and similar in both techniques.

Fresenius 5008 dialysis monitors were used in post-dilution D-OL-HDF with Autosub® retro-control mode. Dialysate flow was automatically adapted to the blood flow in Autoflow® mode. All patients were treated with high flux polysulfone membrane with an effective surface area of 2.10 m² (ELISIO 21H Nipro® or TS 2.1 SL Toray®) and with an acetate-free concentrate.

Anticoagulation in D-OL-HDF modality was either suppressed (8 patients) either decreased with very low doses of non-fractional heparin for the two others patients. Five of the ten patients were treated with antiplatelet therapy and two were treated with anti-vitamine-K therapy.

Data were collected every month for one year, and compared to the data after 3 months before daily OL-HDF when data were available or to baseline.

Usual hemodialysis parameters were obtained at each dialysis session. Blood samples for biological tests were periodically taken from the arterial line according to the K-DOQI recommendations at midweek session, every month for routinely tests or every 3 months (prealbumin) or 12 months (troponin, β 2m and cholesterol) [16].

The value of single-pool Kt/V_{Daug} ($\text{spKt}/V_{\text{Daug}}$) was estimated using the second generation equation of Daugirdas with measurement of urea concentration at H0 and H2.

Bio-impedancemetry analysis was performed on five patients to assess the corporeal composition with the Body Composition Monitor Fresenius®.

Quantitative variables are expressed as mean and standard deviation (SD). Categorical variables are expressed as percentages. Median and means were compared and when it was significant by bilateral paired Wilcoxon Signed-Ranks Test. The probability $p < 0.05$ was considered statistically significant.

RESULTS

Blood flow was similar for both compared techniques: 362.5 ± 25 mL/min at baseline vs 352.1 ± 10.5 mL/min in D-OL-HDF. The mean value of infusion volumes (Vs) was 74 ± 1.65 L/week in daily OL-HDF and the convection volumes (Vc) was 81 ± 2 L/week.

The dialysis adequacy was similar for both modalities. The mean value of weekly $\text{spKt}/V_{\text{Daug}}$ was 5.8 ± 1.29 at baseline and 6.6 ± 1.18 at 12 months of D-OL-HDF (*ns*). The blood purification of middle Molecular Weight (MW) assessed by β 2m pre-dialysis value, was significantly better after 12 months of daily OL-HDF (Table 2).

The Inter-Dialytic Weight Gain (IDWG) was significantly lower at 12 months in daily OL-HDF (1.12 ± 0.63 kg vs 1.96 ± 0.55 kg, $p < 0.05$). However, the total IDWG per week was similar in both modalities (Table 1).

The predialysis blood pressure (BP) was similar for all patients; six of the ten patients were receiving antihypertensive

Table 1: Clinical characteristics.

	M-3	M0	M+6	M+12	P
Blood Pressure:					
SBP (mmHg)	140 ± 20	143 ± 24	142 ± 21	139 ± 24	ns
DBP (mmHg)	73 ± 9	78 ± 18	74 ± 20	72 ± 17	ns
Weight:					
DW (kg)	65.3 ± 9.2	65.0 ± 9.5	65.6 ± 10.6	65.9 ± 11.6	ns
IDWG (kg)	1.96 ± 0.55	0.84 ± 0.71	0.93 ± 0.57	1.12 ± 0.63	0,01
IDWG (kg/week)	6.1 ± 2.9	6.3 ± 2.6	5.6 ± 3.6	6.5 ± 3.1	ns
BMI (kg/m ²)	22.7 ± 3.2	22.6 ± 3.2	22.9 ± 3.1	23.0 ± 3.1	ns
FTI (kg/m ²)	-	10.9 ± 5.4	-	11.8 ± 4.0	ns
LTI (kg/m ²)	-	11.0 ± 3.3	-	10.3 ± 2.8	ns

Values are expressed as mean ± SD or median.

Abbreviations: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; DW: Dry Weight; IDWG: Interdialytic Weight Gain; BMI: Body Mass Index; FTI: Fat Tissue Index; LTI: Lean Tissue Index.

Table 2: Biological characteristics of the patients.

	M-3	M0	M + 6	M + 12	p
Hématologic parameters:					
Hémoglobin (g/dl)	10.9 ± 1.9	11.2 ± 0.2	11.5 ± 2.4	11.8 ± 0.07	0.036
Ferritinemia (µg/l)	395 ± 140	357 ± 292	325 ± 170	220 ± 390	ns
CS (%)	26.0 ± 6.3	24.5 ± 4.2	26.5 ± 12	29.1 ± 45	ns
EPO doses (UI/kg/week)	195 ± 217	126 ± 110	144 ± 146	190 ± 182	ns
Phosphocalcique metabolism:					
Calcium (mmol/L)	2.11 ± 0.12	2.25 ± 0.23	2.18 ± 0.09	2.26 ± 0.09	ns
Phosphorus (mmol/L)	1.42 ± 0.4	1.38 ± 1.0	1.51 ± 0.14	1.55 ± 0.46	ns
PTH (ng/mL)	360 ± 25	310 ± 12	439 ± 10	487 ± 45	ns
PAL (UI)	77.4 ± 3.5	65.9 ± 5.6	85.2 ± 2.1	89.8 ± 11.3	ns
Nutritional parameters:					
Albumin (g/l)	34.2 ± 2-	34.3 ± 2.2	34.2 ± 0.49	36.6 ± 2.5	0.028
Prealbumin (mg/l)	NA-	0.32 ± 0.0	0.32 ± 0.0	0.34 ± 0.0	ns
Total Cholesterol (g/l)	NA-	4.69 ± 1.9	NA-	4.81 ± 1.55	ns
Cardiovascular parameters:					
Total Protein (g/l)	68 ± 8.4	70.3 ± 1.4	67.9 ± 0.7	71.5 ± 0	ns
BNP (pg/ml)	564 ± 164	462 ± 63	315 ± 36	313 ± 17	0.028
Troponin US (µg/l)	NA-	0.05	NA-	0.05	ns
Hemodialysis parameters:					
Weekly spKt/V _d	5.81 ± 1.29	6.42 ± 1.41	6.49 ± 0.94	6.60 ± 1.18	ns
β2m (mg/dl)	NA-	24.8 ± 1.0	NA-	22.9 ± 2.1	0.035

Values are expressed as mean ± SD.

Abbreviations: CS: Saturation Coefficient; PTH: Parathyroid Hormone; PAL: Alkaline Phosphatase; BNP: Brain Natriuretic Peptide; β2m: Beta2-microglobulin

drugs (one or two different molecules). At the end of the observation time, anti-hypertensive treatment has remained stable for all patients with fully controlled blood pressure (Table 1).

Moreover, the value of Brain Natriuretic Peptide (BNP) monitored every month decreased significantly after one year of daily-OL-HDF treatment from 564.7 ± 164 to 313.5 ± 17 pg/ml ($p < 0.05$).

Left Ventricular Ejection Fraction (LVEF) was evaluated for seven of the ten patients by echocardiographic assessment and compared from baseline to one year of D-OL-HDF. The LVEF was significantly increased from 59.1 ± 9.6 to 68.5 ± 9.0 % ($p < 0.05$) (Figure 1).

During the 12 months study period, the haemoglobin value increased from 10.9 ± 1.9 to 11.8 ± 0.07 g/dl ($p < 0.05$), whereas erythropoietin doses, ferritinemia and saturation coefficient

remained stable (Table 2).

Serum calcium and phosphate were unchanged after 12 months of D-OL-HDF as well as PTH value (Table 2). However, the oral calcium supplementation was disrupted for two of the five patients treated, and three of seven patients stopped their phosphate binder treatment. All patients were supplemented with native Vitamin D as recommended. Hyperparathyroidism was treated with Alfacalcidol® for one patient and with Cinacalcet® for another one. These treatments remained stable all over the study.

The serum albumin increased significantly after 12 months of daily OL-HDF (36.6 ± 2.5 vs 33.73 ± 2.0 g/l) ($p < 0.05$), when the total proteinemia remained stable.

In the same time, dry weight and BMI were unchanged. The bioimpedancemetric analysis displayed a stable Fat Adipose Tissue (FAT) mass as well as a stable Fat Tissue Index (FTI) mass

(Figure 2).

Regarding the daily use of vascular access, we did not observe any increase of thrombosis or stenosis events compared to a three-weekly-HDF treatment.

DISCUSSION

Mortality rates remain high for ESRD patients: more than fifty percents at five years after diagnosis [17]. Also worrying is the health-related quality of life of these patients, a predictive factor for mortality [18]. Publications from Fischbach et al., using D-OL-HDF in children reported a better quality of life, an improvement in nutritional status and a reduction of morbi-mortality [14,15]. These results were found and confirmed in adults by Maduell et al. in a study covering a six months period [10]. The authors showed a better quality of solute clearance of small, middle and high weight molecules in D-OL-HDF comparing to standard OL-HDF and good benefits regarding clinical and biological parameters.

Since Maduell et al., in 2003, there hasn't been any publication regarding this technique in hemodialysis literature, even though the results published by Maduell were very encouraging.

We started to use this modality in our center in 2012 and report in this study the results of 12 months of follow up to confirm Maduell's results.

Despite the lack of analyzed data, daily OL-HDF was very well accepted by the ten patients who reported an increase of their quality of life (less tiredness and a better quality of sleep), a better restless after hemodialysis session and less hypotension episodes. The low duration of hemodialysis session and the lack of anticoagulation allowing a decrease in the vascular access compression time decreased daily impact of hemodialysis treatment.

The quality of solute removal regarding small and middle-sized molecules was similar to the two treatments modalities assessed by the $\text{spKt/V}_{\text{Daug}}$. However, we observed, as described by Maduell et al. [10], a significantly decrease of the predialytic $\beta_2\text{m}$ value. This better elimination of MW-molecules could be explained by higher weekly blood purification with daily convective treatment as well as a lower production of $\beta_2\text{m}$.

In this study, the change from three times a week OL-HDF to D-OL-HDF results in an improvement of the nutritional status.

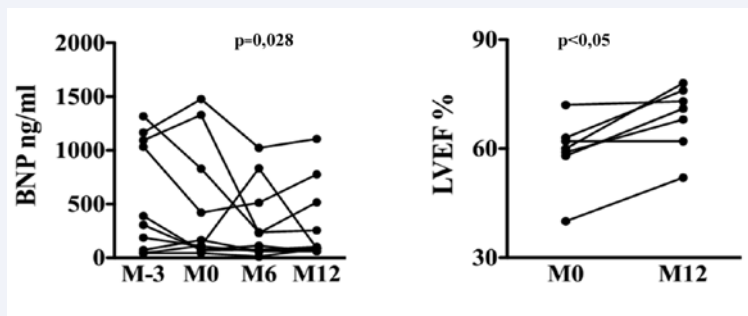


Figure 1 Cardiovascular parameters. BNP (Brain Natriuretic Peptid) and LVEF (Left Ventricular Ejection Fraction) are represented and compared from the beginning and the end of the study.

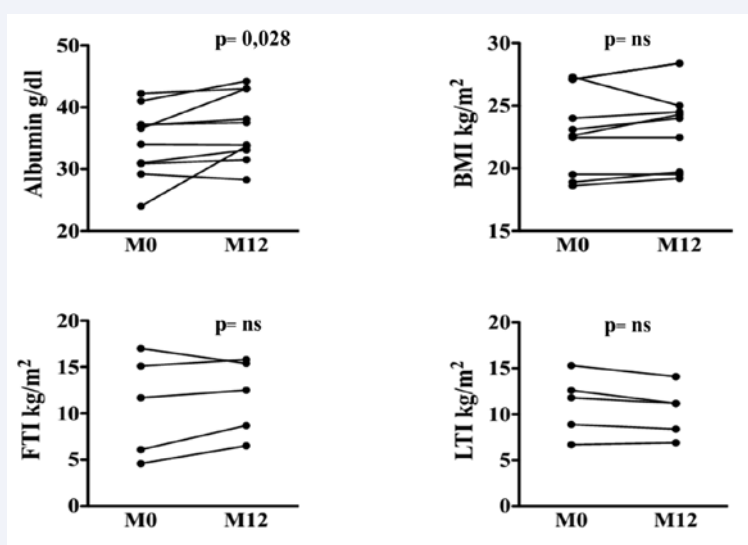


Figure 2 Nutritional parameters are represented between first month (M0) and the end of the study (M12). BMI: Body Mass Index; FFI: Fat Tissue Index; LTI: Lean Tissue Index.

The albumin concentration increases significantly. There is also a tendency for an increase of body weight, body mass index and fat tissue index. These results could be explained by a better appetite noticed in our patients and also observed by Maduell; or by a better solute clearance of the leptin as others middle-sized molecules. This could also be explained by an overestimated dry weight before the beginning of daily OL-HDF; patients could be over-hydrated as suggested by the results of BNP values. Our results are in accordance with the recent data published by the FHN describing an increase of the patients' body weight in frequent (6 times/week) hemodialysis. They also report an increase in estimated adiposity in the 6 times per week group and a relative decrease in the lean body mass which might be explained by the decrease of overweight. This has been associated with improved appetite and increase of protein and caloric intake in frequent hemodialysis modality [20].

It has to be noticed that, D-OL-HDF might decrease albuminemia, as albumin loss is more important during the first two hours of HDF [19]. However, we choose polysulfone membranes with a very low protein loss (<1.5 g/session) to limit this well known risk.

Our cohort of patients displayed a controlled blood pressure before beginning the daily OL-HDF and remained stable all over the study without any change in antihypertensive drugs. It is important to note that most of them were treated with small doses of Beta-blocker or/and Renin-angiotensin system antagonist for their cardioprotective properties and not used for their anti hypertensive effects.

IDWG and the BNP value decreased significantly in short daily OL-HDF. The increase of hemodialysis frequency results in lower volume fluctuations assessed by the lower IDWG and probably a lower overhydration explained by better tolerance to ultrafiltration.

The repercussion on heart is understandable because of the better control of volume variations and extracellular overload increasing the heart post charge, as well as the better nutritional status.

We also showed, by echographic measurements, a significant improvement of LVEF for five patients whereas there was no change for the others (Figure 2). Maduell et al., with magnetic resonance imaging (MRI), described a significant reduction in left ventricular mass at six months [10]. They although explained the reduction of LVM by a better elimination of homocystein, a better control of blood pressure and anemia.

Furthermore, we observed a significant increase in hemoglobin level during the study period while erythropoietin doses remained stable. This result might be explained by several factors such as a better nutritional status, a better blood purification of uremic toxins and at least by the better control of over hydration and IDWG (lower BNP).

In our study, there was no difference in calcemia, phosphoremia and PTH values at 12 months. However, forty percent of patients treated with phosphate binder or with calcium supplementation stopped their treatment. This result is even more relevant that patients have a better appetite as shown by

the increase of albuminemia. The reduction of these medications could have a positive effect on treatment adhesion and obviously on patients' quality of life.

CONCLUSION

D-OL-HDF seems to be an excellent therapeutic alternative to three times a week conventional treatment. In our observational retrospective study, we showed an improvement in nutritional status and a better left ventricular ejection fraction. Patients describe a better quality of life with a better tolerance of dialysis sessions and an improvement of their well-being. These benefits are consistent with those presented by Maduell et al. and should be considered to initiate this hemodialysis modality in a certain type of patients. However, to our knowledge, very few centers are using currently this technique. Further prospective trials are needed to confirm these preliminary results.

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