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Original Article

The Effect of On-line Hemodiafiltration on Improving Cardiovascular Function Parameters in Children on Regular Dialysis

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ABSTRACT. Cardiovascular disease is an important cause of morbidity and mortality in patients undergoing maintenance dialysis, accounting for almost 50% of deaths. Many harmful molecules of the uremic milieu as middle molecules are difficult to remove by conventional hemodialysis (HD). On-line hemodiafiltration (OL-HDF) can cause a considerable clearance of middle molecules and together with its sterile ultrapure infusate may have a favorable effects on inflammation and cardiovascular complications. To assess the effect of OL-HDF on improving the chronic inflammatory state associated with chronic kidney disease and the possible impact of these changes on myocardial function in chronic HD patients. 30 pediatric patients (12 males (40%) and 18 females (60%) with mean age of 11.3 ± 3.2 years) on conventional HD for at least six months were shifted to OL-HDF for another 6 months. Variables for comparison at the end of each period included Hs-CRP, Kt/V as well as ECG, echocardiography, left ventricular mass index (LVMI) and other cardiac functions. On changing from HD to OL-HDF there was a significant decrease in hs-CRP (from 7.9 ± 8.9 to 3.4 ± 3 µg/mL) (P = 0.01) and frequency of diastolic dysfunction (P = 0.04), while systolic function (FS and EF) improved significantly (P = 0.007 and 0.05 respectively) while LVMI did not change. OL-HDF was well tolerated in children with improvement of the systolic function of the myocardium and the overall frequency of diastolic dysfunction.

Introduction

Cardiovascular disease is an important cause of morbidity and mortality in patients undergoing maintenance dialysis, accounting for almost 50% of deaths. Both systolic and/or diastolic functions may be impaired. Overall, the prevalence of heart failure is 10 to 30 fold higher among dialysis patients than in the general population.[1] Given this marked incidence of myocardial dysfunction and poor overall cardiovascular prognosis in dialysis patients, dialysis patients should be evaluated for systolic and diastolic dysfunction.[2]

There is evidence supporting a direct role for

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the uremic milieu and an indirect role for enhanced cardiovascular calcification. Both an increase in diffuse myocardial fibrosis and a reduction in phosphocreatine have been demonstrated in uremic hearts.[3]

Most molecules with potential to affect the function of a variety of cell types within the vascular system are difficult to remove by dialysis. Examples are the larger middle molecular weight molecules and protein-bound molecules. Recent clinical studies suggest that enhancing the removal of these compounds, whether through improving the removal of toxins or the search for pharmacologic strategies blocking responsible pathophysiologic pathways, is beneficial for survival of patients on maintenance hemodialysis (HD).[4]

Furthermore, repetitive exposure to cytokine-inducing substances (pyrogens) results in chronic inflammation, which may significantly contribute to some of the long-term complications in dialysis patients especially cardiovascular one.[5]

On-line dialysis modalities, such as on-line hemodiafiltration (OL-HDF), raise particular concerns because a considerable clearance of so-called middle molecular weight (MMW) substances (5–50 kDa) is obtained.[6]

Moreover, the development of on-line dialysis technology with dialysis fluid passing through an extra stage of purification to produce a sterile ultrapure infusate may have favorable effects on long-term morbidity and even mortality in dialysis patients.[7]

Subjects and Methods

Study design

This study was designed to compare predilution OL-HDF with conventional low-flux HD. Pediatric patients who had been treated previously by conventional HD six months, at Centre of Pediatric Nephrology and Transplantation (CPNT), Cairo University, were switched to OL-HDF with follow up period of another six months thereafter. Data collected following six months of conventional HD and six months of OL-HDF of the same patients for comparison.

Patients

Thirty pediatric patients below 16 year old who were stable on three times weekly renal replacement therapy for at least six months and who had a permanent vascular access capable of delivering a blood flow rate of at least 5 cc/kg/minute, regularly taking their medications (antihypertensive and anti-failure medications) were included in the study. Patients with associated organic cardiovascular disease e.g. rheumatic or congenital heart disease were excluded from the study.

Vascular access

All patients had permanent vascular access in the form of native arteriovenous fistulae or centrally placed venous catheter capable of maintaining blood flow rate above 5 mL/kg/min. for those with arteriovenous fistulae circulatory access was achieved using two 18-gauge needles whether on OL-HDF or on conventional HD.

Dialysis session

OL-HDF was done using Fresenius 4008 dialysis system (Fresenius Medical Care, Bad Homburg, Germany). The same HD configurations, same surface area of the dialyzers using polysulfone membrane-based dialyzer during OL-HDF, identical blood flow rate, dialysate flow rate (500 mL/min) and dialysate temperature of 36°C were used during both conventional HD and OL-HDF. Both during HD and OL-HDF bicarbonate was provided from powder cartridges using the biBAG^{R} system (Fresenius Medical Care) to avoid the risk of bacterial load from bicarbonate concentrates.

Preparation of ultrapure dialysate and substitution fluid

Ultra-pure water is used for the preparation of bicarbonate-containing dialysis fluid, which undergoes one step of ultrafiltration converting it into ultrapure dialysis fluid. The substitution fluid is prepared from the dialysis fluid by one additional step of controlled ultrafiltration, before it is infused pre-filter into the blood. Dialysate and substitution fluid ion concentrations

were as follows: Sodium 140 mmol/L, bicarbonate 32 mmol/L, calcium 1.5 mmol/L, and potassium 2 mmol/L.

The on-line system, ONLINE plus™ (Fresenius Medical Care, Bad Homburg, Germany) is integrated into the dialysis machine (4008 series; Fresenius Medical Care) and consists of two ultrafilters (DIASAFE® plus), an infusate pump module, and disposable infusate lines. Infusate is prepared continuously by double-stage ultrafiltration. Both filters are subjected to automated membrane integrity tests before dialysis, and are replaced after 100 treatments or 12 weeks of use, whichever comes first. Dialysis fluid downstream from the first filter stage enters the dialyser; part of the stream is subjected to cross-flow filtration in the second filter in order to produce infusate.

Technique used and substitution fluid infusion rate

On-line HDF was performed through the predilution method (replacement fluid is infused before (predilution mode) the dialyzer) with re-infusion rate of two-thirds of or equal to blood flow rate guided by TMP to be kept below 200.

Data collection and analysis

Clinical and laboratory data of patients after six months of low-flux HD and OL-HDF were obtained for the sake of comparison. Patients were used as their own control because of the variations in age, size, and underlying disease.

Baseline clinical and anthropometric measures were taken using Egyptian Growth Charts for pediatrics. The mean systolic and diastolic (pre and post dialysis) blood pressure readings of five consecutive sessions were calculated. Blood pressure index is calculated by dividing patient's mean systolic and diastolic blood pressure measurements by the 90th percentile of systolic and diastolic blood pressure, respectively, using blood pressure charts appropriate for the patient's age and sex.[8] Patient is considered hypertensive if his blood pressure index is more than 1.

Standard pre-dialysis blood analyses (i.e. hemo-

Table 1. Blood pressure measurements of the study group.

Variable	HD				OL-HDF				*P* value*
	Min	Max	Mean	SD	Min	Max	Mean	SD	
Pre dialysis SBP (mmHg)	96	155	121	15	97	146	121	11	0.687
Pre dialysis DBP (mmHg)	60	103	78	10	60	96	79	8	0.511
Pre dialysis SBPI	0.87	1.38	1	0.13	0.88	1.37	1	0.11	0.636
Pre dialysis DBPI	0.87	1.37	1	0.14	0.91	1.3	1	0.11	0.505
Post dialysis SBP (mmHg)	80	146	109	12	80	136	109	12	0.682
Post dialysis DBP (mmHg)	50	90	70	8	50	94	71	9	0.377
Post dialysis SBPI	0.75	1.25	0.95	0.1	0.66	1.19	0.96	0.1	0.642
Post dialysis DBPI	0.77	1.2	0.95	0.1	0.66	1.27	0.97	0.14	0.317
Pre dialysis MBPI	0.87	1.37	1	0.13	0.90	1.34	1	0.11	0.75
Post dialysis MBPI	0.77	1.22	0.95	0.1	0.66	1.23	0.96	0.13	0.64
Dialytic change of MBPI	-30	7.65	-10.7	9.2	-26.4	13.7	-10.37	10	0.89

*P-values ≤0.05 are considered significant.

Table 2. Lab data of all cases included in the study.

Variable	HD (midweek, predialysis level)				OL-HDF (midweek, predialysis level)				*P* value*
	Min	Max	Mean	SD	Min	Max	Mean	SD	
HGB (g/dL)	8.1	13.4	10.9	1.4	8	14	11	1.33	0.6
HCT (%)	25.7	40.3	32.5	4	23.8	42	33.3	3.5	0.45
Ca (mg/dL)	7	11	9	0.894	7.42	11.87	8.97	1	0.9
P (mg/dL)	1.5	8.4	5.31	1.67	2	7.7	4.85	1.62	0.27
Ca_P	14.55	75.9	48	16.55	18.2	91.39	44.156	17.81	0.38
ALP (IU/L)	91	2479	778	634	180	4376	821.5	842.8	0.82
BUN (mg/dL)	49	171	75	24	8.6	100	62.48	16.9	0.02
Crea (mg/dL)	3.5	12	6.8	1.76	3.5	10.3	6.7	1.36	0.79
Albumin (g/dL)	3.2	4.7	3.55	0.3	3	4.6	3.66	0.408	0.24
Na (mmol/L)	126	139	135.16	2.51	132	140	135.4	1.92	0.73
K (mmol/L)	4.8	8.7	5.85	0.95	3.9	8	5.71	0.872	0.53
Kt/V	1.05	3.1	1.78	0.48	1.23	2.57	1.82	0.355	0.76
hs-CRP (µg/mL)	0.3	35.7	7.9	8.9	0.2	13	3.4	3	0.01

*P-values ≤0.05 are considered significant.

globin, urea, creatinine, calcium, phosphorus, alkaline phosphatase, sodium, potassium, and serum albumin) were performed on samples collected before dialysis at a mid-week dialysis session.

Urea kinetic using equilibrated Kt/V_{urea} was calculated from pre- and post-treatment urea concentrations according to Daugirdas equation.[9]

hs-CRP: Determination of hs-CRP levels using Accubind® kits (MonobindInc, Lake Forest, CA, USA) using immunoenzymometric assay. As regards the risk of developing atherosclerotic cardiovascular disease, patients were classified as having low risk (CRP <1.0 µg/mL), normal risk (CRP = 1-3) µg/mL, or high risk (CRP >3.0 µg/mL).[10]

ECG recording: Using 12 leads ECG for evidence of arrhythmia, ischemia or chamber enlargement. ECG was done on a mid-week dialysis day following the session of HD or OL-HDF.

Echocardiography: Assessment of myocardial function through echocardiographic evaluation of left ventricular systolic function by determination of fractional shortening, and ejection fraction. Patient was considered to have systolic dysfunction if he had either fractional shortening below 28%, or border-line fractional shortening with manifestations of left ventricular failure.[11] Furthermore, a Doppler sample volume is placed at the mitral valve leaflet tips and left ventricular diastolic function was assessed through determination of mitral deceleration time (DT), Doppler mitral inflow velocity determination including early diastole/atrial contraction maximal velocity ratio (E/A ratio) was also obtained. Accordingly, patients were categorized as either having normal, impaired left ventricular relaxation (E/A<1, or DT>275 msec) or restrictive pattern (E/A>2.5, or DT<110 msec).[11] Left ventricular internal diameter in diastole (LVIDD), posterior wall thickness in diastole (PWTD), and interventricular septum thickness in diastole (IVSTD) were measured and left ventricular mass index (LVMI) was calculated using the equation proposed by the American Society of Echocardiography (ASE):

$$LVMI = 0.8\ (1.04\ [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3] + 0.6\ g$$

Then LVMI is indexed to the patient's body surface area. Left ventricular hypertrophy (LVH) is considered present in children when the LVMI is greater than 103 g/m^2 in males and greater than 84.2 g/m^2 in females, or if the IVSTD is above the normal value for patient's BSA and weight using normal echocardiographic values chart.[11]

Echocardiography was performed by the same operator, on a mid-week dialysis day following the session of OL-HDF and conventional HD. Echocardiographic assessment was

Table 3. ECG and echocardiographic findings in the study group (n = 30).

Variable	HD				OL-HDF				*P* value*
ECG finding	Frequency		Percentage (%)		Frequency		Percentage (%)		
Low voltage	3		10		1		3.33		0.15
T wave abnormality	2		6.67		0		0		0.08
LVH ± strain pattern	4		13.33		3		10		0.34
Echocardiography	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	
FS	27	52	35	5.6	29	60	39	6	0.007
EF	54	89	68	8.5	57	93	72	8	0.05
LVMI	25.7	214	96.5	34	32.3	156.1	93.5	33.6	0.73
DT	32	165	99.8	37	68	192	116	30.6	0.07
E/A ratio	0.66	3.59	1.69	0.7	0.5	3.6	1.56	0.6	0.46

**P*-values ≤0.05 are considered significant.

done by means of Hewlett Packard Sonos 5500® echocardiography system (Hewlett Packard, Palo Alto, CA, USA) immediately following the end of the dialysis session, using S4 and S8 ultraband cardiac transducers with frequency range of 2-4 MHz and 3-8 MHz respectively. Assessment was done through apical 4 chamber view and long axis left parasternal view.

A written informed consent was taken from patients' care providers prior to the study. The current study agrees with the Declaration of Helsinki and its revisions and it was approved by the committee on human experimentation in the Center of Pediatric Nephrology and Transplantation (CPNT), Cairo University Children Hospital, and received as well, the approval of the research and scientific committee of the general pediatric department, Cairo University.

Results

The study included 30 patients on regular HD; 12 males (40%) and 18 females (60%) with mean age of 11.3 ± 3.2 years (range from 4 to 16 years). These patients were on HD with mean duration of 53 ± 32 months (range from 6 to 147 months). The distribution of primary renal disease among the study group is summarized in Figure 1.

hs-CRP level during OL-HDF was 3.4 ± 3 µg/mL (range from 0.2 to 13 µg/mL) compared to 7.9 ± 8.9 (range from 0.3 to 35.7 µg/mL) during HD (*P* = 0.01). The frequency of those with high risk of developing atherosclerotic cardiovascular disease (using increased hs-CRP as a marker for this risk), was 18 patients (60%) during HD compared to 9 patients (30%) during OL-HDF (*P* = 0.01).

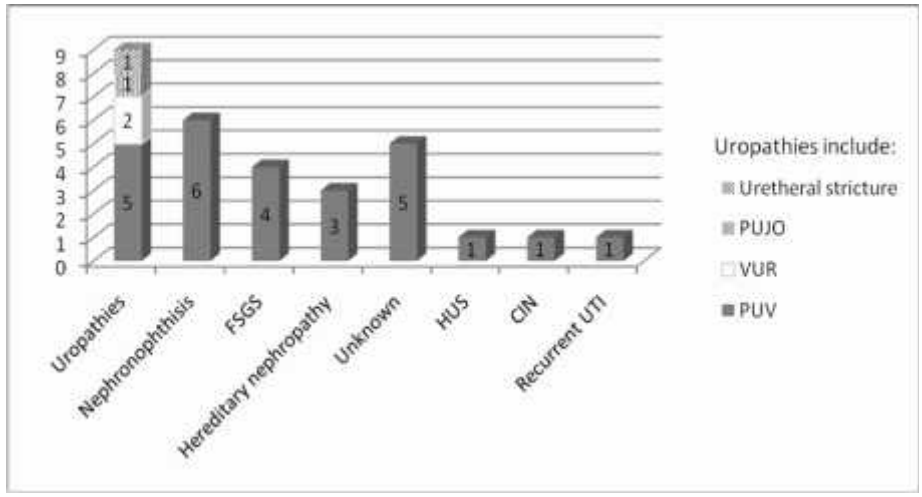

Figure 1. Primary renal disease distribution among the study group.

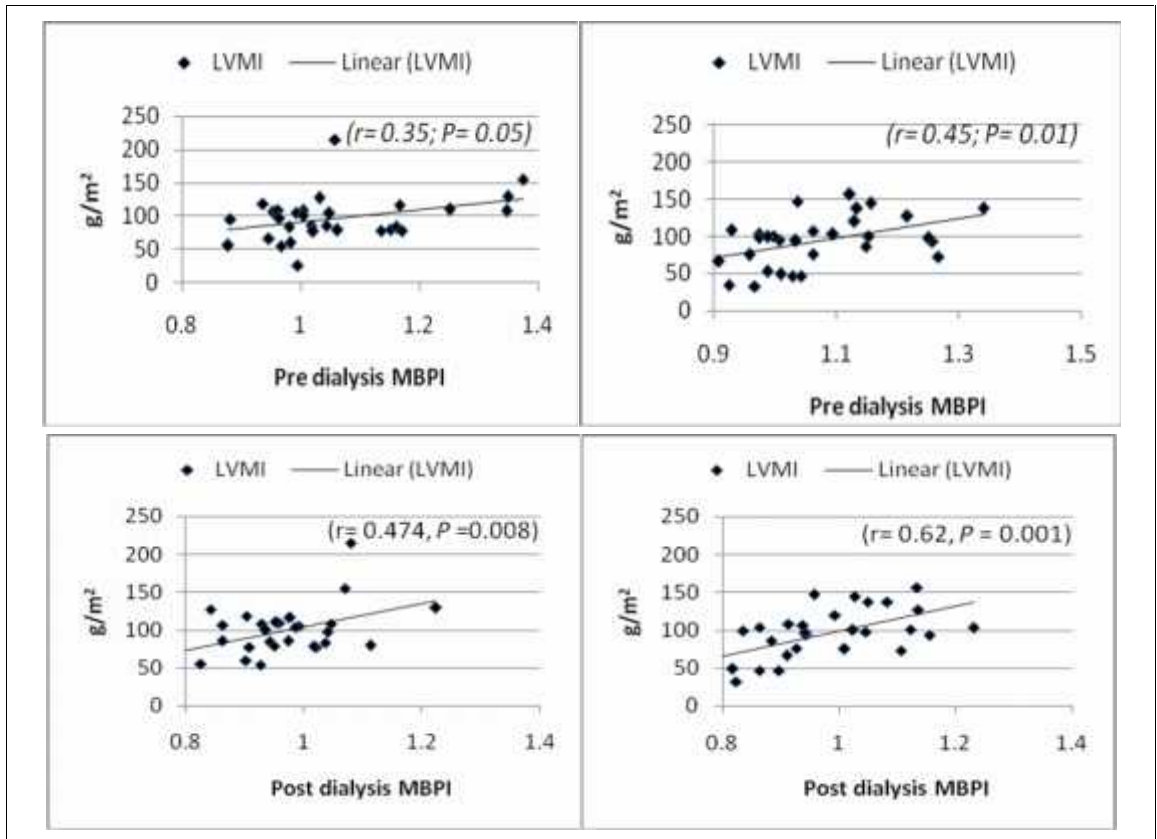

Figure 2. Correlation between MBPI and LVMI both during HD (left) and OL-HDF (right)

Evaluation of the cardiovascular system

Echocardiographic assessment results and ECG abnormalities are summarized in Table 3. There was a significant improvement in systolic function (FS) when changing to OL-HDF while diastolic dysfunction may falsely appear unchanged. Diastolic dysfunction encompasses impaired left ventricular relaxation (where E/A<1) or restrictive pattern (where E/A >2.5) while normal range of E/A ratio lies between "1:2.5". When comparing mean E/A ratio of the study group as a whole, ratios below 1 may counteract those above 2.5 and falsely seems as if there is no diastolic dysfunction among the study group as a whole. On the other hand, studying the cases separately showed that the frequency of diastolic dysfunction in the form of decreased relaxation or restrictive pattern (n = 6, and n = 5 respectively) during HD is greater than those during OL-HDF (n = 4, and n = 1 respectively) (P = 0.04 for both). There was significant improvement in the overall frequency of patients without diastolic dysfunction (n = 25) during OL-HDF compared to the frequency during HD (n = 19) (P = 0.003).

In the current study, LVMI, as an indicator for LVH, decreased non significantly during OL-HDF than during HD (P = 0.73), also there was no significant change in the frequency of patients with LVH during HD (n = 18) and OL-HDF (n = 19) (P = 0.39).

Also, there was positive correlation between pre and post dialysis MBPI and LVMI, both during HD and OL-HDF (Figure 2).

Discussion

Systolic function of the myocardium improved in this study, as shown by significant improvement in FS and EF. As for the myocardial diastolic function, we found that both indices of diastolic function used (DT and E/A ratio) lie within normal range and without significant difference between HD and OL-HDF,

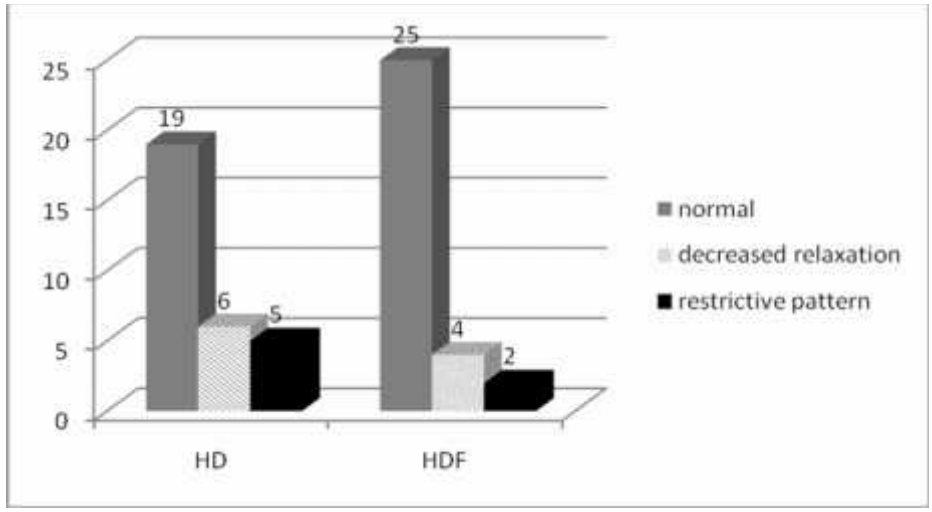

Figure 3. Frequency of myocardial diastolic dysfunction among the study group.

but there was a significant reduction in the overall frequency of patients with diastolic dysfunction during OL-HDF compared to HD. In his review of the literature, Locatelli et al found that evidence supports that HDF is associated with improved myocardial function. This was based on what Teo et al found in his randomized crossover study where he showed that higher convective transport obtained by HDF was associated with improved myocardial function in both the short and the long term with significantly higher ejection fraction and fractional shortening on HDF than on HD.[12,13] The Cochrane researchers reviewing 20 randomized controlled studies done on 657 patients until 2006 were unable to demonstrate whether convective modalities including OL-HDF, have significant advantages over HD as regards clinically important outcomes of mortality, dialysis-related hypotension and hospitalization.[14] Nevertheless the authors mentioned that the studies were generally small with suboptimal quality. In a more recent large study on 906 patients equally subdivided into equal groups, HD (n = 450) and OL-HDF (n = 456), Maduell F and colleagues showed that OL-HDF had a 33% lower risk of cardiovascular mortality [hazard ratio HR, 0.67; confidence interval (95% CI),0.44-1.02; *P* = 0.06], and a 30% lower risk of all-cause mortality [(HR), 0.70; 95% confidence interval (95% CI)], 0.53-0.92; *P* = 0.01)[15]

Another recent meta analysis of 65 trials (29 crossover and 36 parallel-arm) done on 12,182 patients, convective therapy showed a significant decrease in cardiovascular mortality (RR 0.84; 95% CI 0.71, 0.98, *P* = 0.03), but a non significant decrease in all-cause mortality [RR 0.88; 95% confidence interval (CI) 0.76, 1.02, *P* = 0.09] and no change in cardiac morpohological parameters.[16]

In our study, the improvement in the systolic and diastolic myocardial function couldn't be attributed to changes in hemoglobin or hematocrit levels that were proved to be significantly unchanged. Also it couldn't be attributed to changes in blood pressure because all values and calculated indices proved to be also statistically unchanged. Many authors also support the evidence that there is no change in blood pressure values between convective (i.e. OL-HDF) and diffusive (i.e. low flux dialysis) therapies.[17-20] This improvement also couldn't be attributed to change in anti-failure medications (that actually became less during OL-HDF but not statistically significant).

Hs-CRP and chronic inflammation

Despite there was no statistically improvement in Kt/V during HDF as compared to HD, there was significant improvement in predialysis BUN level. This could be due to the

improvement of the chronic inflammatory state, thus reducing the rate of catabolism and urea formation. Similar results were found in the RISCAVID study[21] and others.[17,20]

In the current study, there was significant reduction of hs-CRP during OL-HDF compared to HD. The frequency of patients with elevated hs-CRP during OL-HDF was also significantly lower compared to those on HD. This may be attributed to the observation that OL-HDF combines the use of high-flux synthetic membrane with low bioreactive profile and the use of ultrapure dialysis fluid. This combination is recognized as beneficial in reducing the bioactivation (circulating cells and protein systems) induced by blood–hemodialyzer interaction.[22]

Panichi et al showed in their analysis of the results from the RISCAVID study that patients with combined high levels of CRP and pro-inflammatory cytokines showed an increased risk for cardiovascular and all-cause mortality. Multivariate analysis adjusted for comorbidity and demographic characteristics showed CRP as the most powerful mortality predictor (P <0.001) followed by IL-6.[21]

On-line-HDF was well tolerated and no significant difference in blood pressure change during dialysis session during HD and OL-HDF was found indicating that OL-HDF does not cause hemodynamic changes more than HD. Some researchers found that OL-HDF can be performed safely and for extended period up to six years.[18]

There are some limitations to our study. First, the small number of patiens limiting the power of the study and its conclusions. Second, this study was a short-term study and prolonging the study period may result in more improvement in some variables needing long time to change such LVMI. Finally, we could not elucidate the exact mechanism by which OL-HDF could be associated with better myocardial function than standard HD. However, several explanations may be proposed: the removal of a wider spectrum of uremic solutes, improved intradialytic haemodynamic stability and finally the combination of high-flux synthetic, biocompatible membranes with ultrapure dialysis fluid.[23]

Conclusion

In this study we demonstrated that the use of OL-HDF in pediatric patients with end stage renal disease resulted in improvement of the systolic function of the myocardium. Also, there was significant improvement in the overall frequency of diastolic dysfunction. LVMI remained unchanged all through the study period however longer follow up duration may be needed before evaluating the impact of OL-HDF on LVH.

At last, the value of OL-HDF in improving the chronic inflammatory state commonly seen in dialysis patients could add to the beneficial effects of OL-HDF in cutting down the frequency of different cardiovascular morbidities.

Conflict of Interest

No conflict of interest is present in our work and no grants were provided for this study.

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