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Case Report

The Effect of Hemodiafiltration on Inflammatory Biomarkers in Comparison to High Flux Dialyzers in Prevalent Hemodialysis Patients

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ABSTRACT

Introduction Inflammation in patients with ESRD undergoing HD is an increasing concern for physicians and has been related to increase the rates of morbidity and mortality. Interestingly, patients with ESRD in conventional HD have frequent infections and a suboptimal response to vaccines; this is probably related to an immune inflammatory disorder associated either with uremia and /or nutritional status. In addition to CRP, which seems to be the most important marker for the identification and control of inflammation in clinical practice, many other markers are also available for the evaluation of inflammatory state. Decreased renal clearance clearly accounts for higher levels of circulating cytokines, although increased production has also been described. Hemodiafiltration has been shown to improve cardio-protection and the immunologic system and reduces infection and mortality compared with conventional HD. A recent study showed that hemodiafiltration compared with conventional HD reduced the risk of mortality in ESRD patients. Analysis of pooled individual participant data from randomized controlled trials has shown survival benefits of high volume-HDF on all-cause mortality and especially cardiovascular mortality rate. The mechanisms that lead to improved outcomes are not clear, but it is thought that HDF may reduce the production of inflammatory mediators through the use of biocompatible dialysers and ultra-pure dialysate and also improve clearance of larger molecular weight substances, many of which are associated with oxidative stress, inflammation and endothelial dysfunction. Objective The aim of this study is to detect, prospectively, the effect of 3 months dialysis with Hemodiafiltration on inflammatory and nutritional biomarkers in comparison to conventional dialysis with high flux dialyzer in stable HD patients. Patients and methods 30 adults aged 20-75 years who were selected from Dialysis Unit, Kobary El-Kobba Military Hospital. 30 male patients known to have chronic kidney disease and are on dialysis with high flux dialyzer more than 3 months were divided into 2 groups:15 Patients are shifted to be on dialysis with HDF and 15 Patients are continued to be on Regular Hemodialysis with high flux dialyzer. Full medical history and clinical examination. Anthropometric measurements and Laboratory investigations including Complete Blood Picture (WBCs, platelets, Hb), Coagulation profile PT, PTT&INR, Liver function tests (ALT, AST, T. Bilirubin and S. Albumin), Lipid profile (Triglycerides, total cholesterol, VLDL), S. creatinine, BUN, Na, K, Uric acid, Total Proteins, Serum Calcium, Serum Phosphorus, PTH, Serum ferritin, High sensitivity CRP (Enzyme- Linked Immunosorbent Assay (ELISA)) and IL6 (ELISA).

1. Introduction

Inflammation has been recognized as an essential part of chronic kidney disease (CKD). In the late 1990s and it was linked to cardiovascular disease, protein-energy wasting, and mortality. In the Chronic Renal Insufficiency Cohort (CRIC) study, biomarkers of inflammation (IL-1β, IL-1 receptor antagonist, IL-6, TNF-α, CRP, and fibrinogen) were inversely associated with the measures of kidney function and positively with albuminuria (Gupta et al., 2012).

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Despite recent advances in CKD and end-stage renal disease (ESRD) management, morbidity and mortality in this population remain high. Persistent low-grade inflammation has been recognized as an important component of CKD, playing a unique role in its Pathophysiology and being accountable in part for cardiovascular and all-cause mortality, as well as contributing to the development of protein-energy wasting (Akchurin and Kaskel, 2015).

CKD and especially dialysis patients are prone to additional inflammatory stimulations due to infectious and thrombotic events such as, catheter-related bloodstream infections, access site infections, thrombosed fistulas and grafts, and episodes of peritonitis in PD patients (Ruospo et al., 2014).

As renal function deteriorates, worsening of appetite and a decline in the nutritional state is frequently observed in patients with chronic kidney disease (CKD). Protein Energy Wasting (PEW) describes a state of decreased body protein and energy stores. PEW is defined as the presence of three out of the following four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake (Pieter and Denis, 2015).

Pro-inflammatory cytokines may directly cause anorexia via influence on the brain. In addition, inflammatory markers, particularly IL-6, may be associated with depression in CKD and ESRD, which by itself is a predictor of morbidity and mortality (Taraz et al., 2014).

Inflammation has been proved to have a role in the pathophysiology of anemia and bone disorders. TNF-alpha is an inducer of the NF-κB ligand (RANKL) which is a key trigger of osteoclast activation and bone resorption (Panuccio et al., 2012).

For ESRD patients, two main approaches to decrease inflammatory load related to the dialysis procedure were proposed. First, elimination of factors triggering inflammation, second, removal of inflammatory mediators. Interventions that were tested include the use of biocompatible membranes, purity standards for hemodialysis (HD) water, ultrapure dialysate, increased dialysis frequency, and Hemodiafiltration (Santoro and Mancini, 2014).

Recent meta-analysis demonstrated that the use of ultrapure dialysate in HD patients results in a decrease in markers of inflammation and oxidative stress, an increase in serum albumin and hemoglobin and a decrease in erythropoietin requirement. Hemodiafiltration may decrease inflammatory activity via additional clearance of middle molecules by convection (den Hoedt et al., 2014).

Objective

The aim of this study is to detect, prospectively, the effect of 3 months dialysis with Hemodiafiltration on inflammatory and nutritional biomarkers in comparison to conventional dialysis with high flux dialyzer in stable HD patients.

Patients and Methods

The present study was conducted on a random sample of 30 adults aged 20-75 years who were selected from Dialysis Unit, Kobary El-Kobba Military Hospital. 30 male patients known to have chronic kidney disease and are on dialysis more than 3 months were divided into 2 groups: 15 Patients are known to be on dialysis with HDF and 15 Patients are known to be on conventional dialysis with high flux dialyzer

Methods

All patients were subjected to the following:

1. Full medical history and clinical examination.

2. Anthropometric measurements and Laboratory investigations includingComplete Blood Picture (WBCs, platelets, Hb), Coagulation profile PT, PTT&INR, Liver function tests (ALT, AST, T. Bilirubin and S. Albumin), Lipid profile (Triglycerides, total cholesterol, VLDL), S. creatinine, BUN, Na, K, Uric acid, Total Proteins, Serum Calcium, Serum Phosphorus, PTH, Serum ferritin, High sensitivity CRP (Enzyme- Linked Immunosorbent Assay (ELISA)) and IL6 (ELISA).

Sampling

Samples were collected from each patient under complete aseptic conditions using sterile vacutainers and divided as follows:

Two ml PB samples were obtained on ethylene diamine tetra-acetic acid, dipotassium salt (K2-EDTA) in vacutainer tubes (final concentration of 1.5 mg/mL) for CBC.

Two ml PB samples were obtained on citrate in vacutainer tubes for PT, PTT and INR.

Two ml PB samples were obtained on gel vacutainer tubes for other electrolytes, hs CRP and Il6.

ELISA for hs CRP:

Principle:

Hs CRP Human ELISA kit is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of Human CRP in serum, plasma, cell culture supernatants.

This assay employs an antibody specific for Human CRP coated on a 96-well plate. Standards and samples are pipetted into the wells

and CRP present in a sample is bound to the wells by the immobilized antibody. The wells are washed and biotinylated anti-Human CRP antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and color develops in proportion to the amount of CRP bound. The Stop Solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm (Huang Y et al., 2019).

ELISA for IL6:

Principle:

A monoclonal antibody specific for IL-6 has been coated onto the wells of the microtiter strips provided. Samples, including standards of known IL-6 concentrations, control specimens or unknowns are pipetted into these wells. During the first incubation, the standards or samples and a biotinylated monoclonal antibody specific for IL-6 are simultaneously incubated. After washing, the enzyme Streptavidin-HRP, that binds the biotinylated antibody is added, incubated and washed. A TMB substrate solution is added which acts on the bound enzyme to induce a colored reaction product. The intensity of this colored product is directly proportional to the concentration of IL-6 present in the samples (Quan B et al., 2019).

Statistical Analysis:

Data were collected, revised, coded and entered to the statistical package for social science version 21.0. Quantitative data were expressed as mean ± standard deviation (SD).

Analytical statistics:

Independent test (t-value) was used for comparing quantitative data.

Pearson-correlation co-efficient(r) was used in correlation studies.

Significance was evaluated as follows:

P value 0.05 non-significant (NS).

P value < 0.05 significant (S).

P value < 0.01 highly-significant (HS).

Results

The results of the present study are shown in tables (1-6). The study was conducted on 30 patients with chronic kidney disease on regular dialysis. The patients were divided into two groups A representing patients on hemodiafiltration (n=15) and group B representing patients on conventional dialysis with high flux dialyzer (n=15).

Table (1): Comparison between group A and group B as regard some demographic and biochemical data:

	Group A (n = 15)			Group B (n = 15)			t	P	Sig.
	Mean	SD	Median	Mean	SD	Median			
Age (years)	58.7Â	13.3	62.0	57.3	16.8	63.0	0.811	> 0.05	NS
Weight (kg)	88.3	13.5	87.0	80.3	9.4	83.0	0.070	> 0.05	NS
BMI (%)	29.6Â	3.8	30.0	26.4	3.6	27.0	0.026	< 0.05	**S**
Hb (gm/dl)	10.3Â	1.2	10.3	10.6	1.3	10.7	0.386	> 0.05	NS
WBCS (x 10^3)	6.7Â	3.6	5.6	7.1	2.9	6.7	0.714	> 0.05	NS
PLT (x 10^3)	205.2Â	108.5	196	197.2	87.1	177	0.825	> 0.05	NS
SGOT (U/l)	25.7Â	15.3	22.0	24.0	10.5	26.0	0.721	> 0.05	NS
SGPT (U/l)	30.7Â	12.3	27.0	30.9	9.9	30.0	0.961	> 0.05	NS
PT (sec)	12.5Â	0.3	12.4	12.3	0.1	12.3	0.074	> 0.05	NS

PTT (sec)	40.3Â	4.8	42.0	33.9	5.9	34.0	0.003	< 0.01	**HS**
INR	1.2	0.2	1.0	1.1	0.1	1.1	0.129	> 0.05	NS
T. Bil (mg/dl)	0.8Â	0.3	0.9	1.0	0.5	0.9	0.128	> 0.05	NS
T. proteins(gm/dl)	7.0Â	1.1	6.7	7.3	1.2	6.9	0.413	> 0.05	NS
Albumin (gm/dl)	4.2Â	0.3	4.2	4.1	0.7	4.1	0.556	> 0.05	NS
BUN (mg/dl)	57.5Â	12.8	53.3	63.4	14.0	61.2	0.240	> 0.05	NS
Creatinine (mg/dl)	10.6Â	2.4	10.0	10.8	2.1	10.8	0.819	> 0.05	NS
K (meq/l)	4.8	0.7	5.0	4.8	0.6	4.8	0.916	> 0.05	NS
Uric acid (mg/dl)	5.4	2.2	5.8	5.0	2.0	5.4	0.577	> 0.05	NS
Phosphorus (mg/dl)	5.1	1.2	4.8	5.6	1.0	5.4	0.233	> 0.05	NS
Ca (mg/dl)	9.4	1.1	9.6	9.1	0.9	9.3	0.428	> 0.05	NS
Ferritin (mg/dl)	224.1Â	107.6	250.0	153.9	112.3	91.0	0.091	> 0.05	NS
PTH (pg/ml)	480.7Â	211.6	400.0	393.9	119.7	380.0	0.178	> 0.05	NS

Table (1): Shows a comparison between group A and group B as regard some demographic and biochemical data which revealed:

A high statistical significant difference (P < 0.01) was found regarding PTT 40.3±4.8 sec. in group A while it is 33.9±5.9 sec. in group B, a statistical significant difference (P < 0.05) was found regarding BMI 29.6±3.8 % in group A while it is 26.4±3.6 % in group B and no statistical significant difference (P > 0.05) was found as regard the other demographic and biochemical data.

	Group A (n = 15)			**Group B (n = 15)**			**t**	**P**	**Sig.**
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**			
CRP before 3 months (mg/dl)Â	87.7	44.9	92.5	109.2	41.8	115.0	0.125	> 0.05	NS
CRP after 3 months (mg/dl)Â	63.5	40.9	40.0	73.4	33.2	65.0	0.039*	> 0.05	**S**
IL6 before 3 months (mg/dl)Â	162.0	77.8	150.0	188.0	147.1	170.0	0.550	> 0.05	NS
IL6 after 3 months (mg/dl)Â	85.3	37.6	80.0	156.7	151.9	120.0	0.048*	> 0.05	**S**

Table (1): Shows a comparison between group A and group B as regard some demographic and biochemical data which revealed:

A high statistical significant difference (P < 0.01) was found regarding PTT 40.3±4.8 sec. in group A while it is 33.9±5.9 sec. in group B, a statistical significant difference (P < 0.05) was found regarding BMI 29.6±3.8 % in group A while it is 26.4±3.6 % in group B and no statistical significant difference (P > 0.05) was found as regard the other demographic and biochemical data.

Table (3): Comparison between CRP before and after 3 months in group A using Chi-Square test:

CRP			
		Before 3 months	**After 3 months**
Group A (n = 15)	**N.**	15	15
	%	50%	50%
X^2		0.267	
P		<0.05	
Sig.		**S**	

regarding CRP.

Table (3): Shows comparison between CRP before and after 3 months in group A using Chi-Square test which revealed:
A statistical significant difference (P <0.05) was found regarding CRP.

CRP			
		Before 3 months	After 3 months
Group B (n = 15)	N.	15	15
	%	50%	50%
X^2	0.364		
P	> 0.05		
Sig.	NS		

Table (5): Comparison between IL6 before and after 3 months in group A using Chi-Square test:

Table (5): Comparison between IL6 before and after 3 months in group A using Chi-Square test:

IL6			
		Before 3 months	After 3 months
Group A (n = 15)	N.	15	15
	%	50%	50%
X^2	0.515		
P	<0.05		
Sig.	S		

Table (5): Shows comparison between IL6 before and after 3 months in group A using Chi-Square test which revealed:

A statistical significant difference (P <0.05) was found regarding IL6.

Table (6): Comparison between IL6 before and after 3 months in group B using Chi-Square test:

IL6			
		Before 3 months	After 3 months
Group B (n = 15)	N.	15	15
	%	50%	50%
X^2	0.545		
P	> 0.05		
Sig.	NS		

Table (6): Shows a comparison between IL6 before and after 3 months in group B using Chi-Square test which revealed:

No statistical significant difference (P > 0.05) was found regarding IL6.

Discussion

Inflammation in patients with ESRD undergoing HD is an increasing concern for physicians and has been related to increase the rates of morbidity and mortality. Interestingly, patients with ESRD in conventional HD have frequent infections and a suboptimal response to vaccines; this is probably related to an immune inflammatory disorder associated either with uremia and /or nutritional status (Nistor et al., 2015).

In addition to CRP, which seems to be the most important marker for the identification and control of inflammation in clinical practice, many other markers are also available for the evaluation of inflammatory state. Decreased renal clearance clearly accounts for higher levels of circulating cytokines, although increased production has also been described (Rosengren et al., 2013).

Hemodiafiltration has been shown to improve cardio-protection and the immunologic system and reduces infection and mortality compared with conventional HD. A recent study showed that hemodiafiltration compared with conventional HD reduced the risk of mortality in ESRD patients (Peters et al., 2016).

Analysis of pooled individual participant data from randomized controlled trials has shown survival benefits of high volume-HDF on all-cause mortality and especially cardiovascular mortality rate (Peters et al., 2016). The mechanisms that lead to improved outcomes are not clear, but it is thought that HDF may reduce the production of inflammatory mediators through the use of biocompatible dialysers and ultra-pure dialysate and also improve clearance of larger molecular weight substances, many of which are associated with oxidative stress, inflammation and endothelial dysfunction (Nube, 2016).

The aim of this study is to detect, prospectively, the effect of 3 months dialysis with Hemodiafiltration on inflammatory and nutritional biomarkers in comparison to conventional dialysis with high flux dialyzer in stable HD patients.

This study was conducted on two groups:

Group (A) and Group (B) with comparable some demographic and biochemical data; there were not statistically significance between the group A and group B (P > 0.05) as regard age, weight, hemoglobin, WBCs, platelets, AST, ALT, PT, INR, total bilirubin, total protein, serum albumin, BUN, creatinine, potassium, uric acid, phosphorous, calcium, ferritin and parathormone except for BMI and PTT whereas group A had significantly higher PTT levels (40.3±4.8 sec. versus 33.9±5.9 sec. respectively; P < 0.01) and also group A had significantly higher BMI levels (29.6±3.8 % versus 26.4±3.6 % respectively; P < 0.05) when compared to the group B. These results are at variance with Antonio and Elena 2014 who have reported no actual differences present with the raw data; in the trend analysis, only a natural data log for the two crucial variables shows a subtle difference over time.

Another result of the study by den Hoedt et al.,2014 that might arouse a certain degree of bewilderment is the behavior of the serum albumin, faced with a lower degree of inflammation, the level of albumin should have remained stable in OL-HDF, whereas we can see it drop in the same way as in HD. This result is seen as positive by Antonio and Elena 2014 and is interpreted as the practical demonstration that OL-HDF does not diminish the albumin assets via an intradialytic loss. OL-HDF could thus be considered a safe technique in regard to the risk of protein malnutrition induced by the treatment. And thus, if it is true that, OL-HDF reduces inflammatory activity, the reduction in albumin over time may in HD be tied to the chronic inflammatory state, while in OL-HDF it is the expression of the chronic loss, that comes about to a greater extent in OL-HDF than in HD.

The present study showed hs-CRP levels were significantly lower in group A compared to group B (63.5±40.9 mg/dl versus 73.4±33.2 mg/dl respectively; P < 0.05), also IL6 levels were significantly lower in group A compared to group B (85.3±37.6 mg/dl versus 156.7±151.9 mg/dl respectively; P < 0.01) after 3 months and no statistical significant difference (P > 0.05) was found as regard those inflammatory markers before 3 months. These results agree with a study based on a large series of data obtained in the course of the Convective Transport Study (CONTRAST), den Hoedt et al., 2014 found that, in the long term, CRP and IL-6 levels increased in patients treated with HD, while both CRP and IL-6 were almost stable in patients treated with OL-HDF, the authors state that long-term HDF with ultrapure dialysate seems to reduce inflammation. This is the first ever clinical trial demonstrating such a difference, and also proposed that long-term hemodiafiltration with ultrapure dialysate might reduce inflammatory activity over time.

The great merit of the study by den Hoedt et al., 2014 is that the data, coming from a large prospective, randomized study such as CONTRAST, were obtained over a period of 3 years, long enough to highlight trends of a minimal degree. However, changes in CRP and IL-6 are rather marginal, with a difference of just 20% in the rate of CRP increment, corresponding to an increase in CRP from 1mg/l to 1.2mg/l.

Ping et al., 2016 observed an increase in hs-CRP level after a single and short-term HD sessions, however, in OL-HDF patients, the level of hs-CRP remained relatively stable after 2-week dialysis. In addition, their study found a decrease in IL-6 level in OLHDF patients, while no change in HD patients, after 2-week dialysis sessions which suggest a beneficial effect of short-term OL-HDF in amelioration of inflammation.

Moreover Ağbaş et al., 2018 suggest that HDF achieves superior removal of middle molecules compared to HD. Interleukin-6 and IL-10, that are pro-inflammatory and anti-inflammatory cytokines respectively, are middle molecules and thus expected to be removed in HDF.

However, Morad et al., 2014 study has reported conflicting results, with some reporting reduced levels IL-6, and increased IL-10, whereas Filiopoulos et al., 2008 demonstrate no significant decrease on HDF compared to HD.

Conclusion

The present study revealed that there was a significant decrease in CRP and IL6 in patients on HDF compared to patients undergoing hemodialysis with high flux dialyzer after 3 months.

Recommendations

The current study recommends that ESRD patients are better to be undergoing hemodiafiltration rather than hemodialysis for its better impact on inflammatory biomarkers.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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