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Study of the Effect of Haemodiafiltration on the CKD-MBD in Regular Haemodialysis Patients

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Abstract: Renal replacement therapy (RRT) replaces nonendocrine kidney function in patients with renal failure and is occasionally used for some forms of poisoning. Techniques include continuous hemofiltration and hemodialysis, intermittent hemodialysis, and peritoneal dialysis. All modalities exchange solute and remove fluid from the blood, using dialysis and filtration across permeable membranes. **In our study**, we studied 100 patients divided into 2 groups. (1) Group (1) included 60 patient were on heamodilysis. (2) Group (2) included 40 patient were on haemodiafiltration. In our study, we found a highly statistical significant difference (P value <0.001) between 2 groups regarding the mean of (PTH). By comparison between the two groups we found a significant difference in The level of Parathyroid Hormone as a high level of PTH with HD in comparison with HDF. In our study, we found a highly statistical significant difference (P value <0.000) between 2 groups regarding the mean of S. Phosphrus and by the way Ca * Po4 level. By comparison between the two groups we found a significant difference in the level of S. Phosphrus as a high level of Po4 with HD in comparison with HDF. Serum phosphate levels >3.5 mg/dl were associated with a significantly increased risk for death. Mortality risk increased linearly with each subsequent 0.5-mg/dl increase in serum phosphate levels. So Our Study prove that there is a great effect of HDF on bone mineral diseases and this effect go in agreement with many studies that encourage use of HDF for CKD-MBD patients. We found a significant difference in the level of Albumin as the level of Albumin with HDF (mean 3.36 ± 0.21) in comparison with HD (mean 3.39 ± 0.21). As we know that Middle molecules, consisting mostly of peptides and small proteins with molecular weight the range of 500-60,000 Da, accumulate in renal failure and contribute to the uraemic toxic state. B2-Microglobulin (B2-MG) with a molecular weight of 11,000 is considered representative of these middle molecules. This convective component of high-flux dialysis can be enhanced in a predictable way by haemodiafi ltration (HDF). In our study, we found by a comparison between the two groups we found a significant difference in the level of B2 Microglobulin as a high level of with HD VS in HDF and this revealed an inverse correlation between the β_2-microglobulin level and the duration of HDF. So Long-term HDF further reduced β_2-microglobulin levels, thus, it may provide an improved modality for renal replacement therapy. So we encourage Long-term HDF which may provide an Optimum modality as renal replacement therapy for prevention of **Carpal Tunnel Syndrome**, HDF can clinically reduce the incidence of dialysis related amyloidosis.

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1. Introduction

Renal replacement therapy (RRT) replaces nonendocrine kidney function in patients with renal failure and is occasionally used for some forms of poisoning. Techniques include continuous hemofiltration and hemodialysis, intermittent hemodialysis, and peritoneal dialysis. All modalities exchange solute and remove fluid from the blood, using dialysis and filtration across permeable membranes.

RRT does not correct the endocrine abnormalities (decreased erythropoietin and 1,25-dihydroxyvitamin D3 production) of renal failure. (Merlino and Piani, 2006).

During dialysis, serum solute (eg, sodium, chloride, potassium, bicarbonate, calcium, magnesium, phosphate, urea, creatinine, uric acid) diffuses passively between fluid compartments down a concentration gradient (diffusive transport). During filtration, serum water passes between compartments down a hydrostatic pressure gradient, dragging solute with it (convective transport). The two processes are

often used in combination (hemodiafiltration). Hemoperfusion is a rarely used technique that removes toxins by flowing blood over a bed of adsorbent material (usually a resin compound or charcoal). (Shalkham et al., 2006).

All forms of RRT except peritoneal dialysis require vascular access; continuous techniques require a direct arteriovenous or venovenous circuit.

The choice of technique depends on multiple factors, including the primary need (eg, solute or water removal or both), underlying indication (eg, acute or chronic kidney failure, poisoning), vascular access, hemodynamic stability, availability, local expertise, and patient preference and capability (eg, for home dialysis). (Storr et al., 2006).

Although the physical and chemical concepts of diffusion and convection are well known, dialysis has been carried out mainly by diffusion during its first four decades. This form of dialysis, hemodialysis (HD), has ensured the survival of millions of patients with advanced kidney disease worldwide and has met the increasing needs generated in the 50 years since dialysis was considered for long-term renal replacement therapy.

The delay in incorporating convection techniques as routine treatment has technological and economic reasons. Hemofiltration (HF) or hemodiafiltration (HDF) modalities require the use of dialyzers of high permeability and, at the same time, monitors with volume control and a dual pump. Replacement fluid is a key constraint on the initial HDF technique, with volumes ranging between 3 and 10 L. The introduction of online HDF techniques using the dialysis fluid itself as a replacement solution has meant a revolution in HD units. It has taken another 10 years to renovate and upgrade water treatment, introduce specific monitors, and incorporate safety filters to ensure ultrapure dialysate (Pyo et al.,2017).

Aim of the Work

The aim of the work is to Study of the role of HDF on the Laboratory Aspect of CKD-MBD compared with Haemodialysis.

2. Patients and Methods

This Study was carried out at The Nephrology Department, at El Sahel teaching hospital, Cairo from August 2019 to March 2020, comparing hemodialysis with long-term hemodiafiltration.

We compared data of (60) hemodialysis (HD) patient and (40) hemodiafiltration (HDF) patient over a period of 9 months. Dialysis parameters (dialysate composition and flow, duration, dialyzer) were the same in the two periods except for the added convection of HDF and a higher tolerated blood flow in HDF.

- **Inclusion criteria*:***
  - Age: 18 Years to 60 Years.
  - Informed consent.
  - Hemodialysis more than six months.
  - Hemodialysis 3 times/week for four hours.

Exclusion Criteria

- Age younger than 18 years.
- Chronic Infection.
- Pregnancy or lactating.
- Life threatening malignancy.
- Previous long-term systemic treatment with immunosuppressive drugs.
- HIV positive.
- Patients assessment:

Patients were be divided into two groups:

- Group1: 60 Patients on Haemodialysis Therapy.
- Group2: 40 Patients on Haemodialysis Therapy.

Table (1): Demographic data for whole group.

		Hemodialysis		HDF		t test	
		Mean	**SD**	**Mean**	**SD**	**p value**	**sig.**
AGE		49.12	11.33	49.51	10.91	0.864	NS
Years of dialysis		9.76	3.97	11.02	4.62	0.148	NS
		N	**%**	**N**	**%**	**Chi square test**	
GENDER	**Female**	31	53.4%	20	48.8%	0.647	NS
	Male	27	46.6%	21	51.2%		
HTN	**No**	21	36.2%	20	48.8%	0.211	NS
	Yes	37	63.8%	21	51.2%		
DM	**No**	42	72.4%	35	85.4%	0.127	NS
	Yes	16	27.6%	6	14.6%		
HCV	**Negative**	48	82.8%	31	75.6%	0.383	NS
	Positive	10	17.2%	10	24.4%		

Statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(SPSS 20).** Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

3. Results

Table (1) shows the demographic data for whole group participating in our study, there were 48 male and 51 female and the age was 49 (41 - 59), 51.2 % had hypertension (n=21) in HDF and 63.8 % (n=37) in HD, 14.6 % were diabetic (n=6) in HDF and 27.6 % (n=16) in HD, 24.4 % were HCV positive (n=10) in HDF and 17.2 % (n=10) in HD.

Table (2): Lab investigations between 2 groups of study.

	Hemodialysis		HDF		t test	
	Mean	**SD**	**Mean**	**SD**	**p value**	**sig.**
CREATININE	6.74	1.79	6.49	1.64	0.472	NS
URR	58.70	11.09	63.02	12.43	0.072	NS
Kt/V	1.31	.10	1.30	.06	0.635	NS
HB	10.43	1.68	10.31	1.36	0.707	NS
HCT	31.41	4.34	30.97	4.39	0.624	NS
Na	136.31	4.02	137.44	3.90	0.167	NS
K	5.13	1.13	5.20	.94	0.758	NS
SR ALBUNIM	3.90	.21	3.36	.21	0.000	S
CA	7.90	.71	7.88	.68	0.891	NS
PO4	5.28	.77	3.83	.41	0.000	S
Ca*Po4	41.65	6.90	30.14	3.72	0.000	S

4. Discussion

The aim of the work is to Study of the role of HDF on the Laboratory Aspect of CKD-MBD compared with Haemodialysis.

We have compared treatment with (60) hemodialysis (HD) patient and (40) hemodiafiltration (HDF) patient over a period of 9 months. Dialysis parameters (dialysate composition and flow, duration, dialyzer) were the same in the two periods except for the added convection of (HDF) and a higher tolerated blood flow in HDF.

Prevention and correction of hyperphosphatemia is a major goal of chronic kidney disease–mineral and bone disorder (CKD–MBD) management, achievable through avoidance of a positive phosphate balance (Becker et al., 2009). To this aim, optimal dialysis removal, careful use of phosphate binders, and dietary phosphate control are needed to optimize the control of phosphate balance in well-nourished patients on a standard three-times-a-week hemodialysis schedule (Angus and Van der Poll, 2013).

Using a mixed diffusive–convective hemodialysis techniques, and increasing the number and/or the duration of dialysis tecniques are all measures able to enhance phosphorus (P) mass removal through dialysis (Shomali et al., 2013).

However, dialytic removal does not equal the high P intake linked to the high dietary protein requirement of dialysis patients; hence, the use of intestinal P binders is mandatory to reduce P net intestinal absorption (Yang et al., 2007). Unfortunately, even a large dose of P binders is able to bind approximately 200–300 mg of P on a daily basis, so it is evident that their efficacy is limited in the case of an uncontrolled dietary P load (Linscheid et al., 2005).

Hence, limitation of dietary P intake is needed to reach the goal of neutral phosphate balance in dialysis, coupled to an adequate protein intake. To this aim, patients should be informed and educated to avoid foods that are naturally rich in phosphate and also processed food with P-containing preservatives (Baghi et al., 2015).

In addition, patients should preferentially choose food with a low P-to-protein ratio. For example, patients could choose egg white or protein from a vegetable source. Finally, boiling should be the preferred cooking procedure, because it induces food demineralization, including phosphate loss (Abbasi et al., 2010). The integrated approach outlined in this article should be actively adapted as a therapeutic alliance by clinicians, dieticians, and patients for an

effective control of phosphate balance in dialysis patients.

In the course of chronic kidney disease (CKD), P serum levels remain within normal limits until the advanced stages of CKD. Therefore, hyperphosphatemia must be considered a very late indicator of P retention (Abbasi et al., 2010). Instead, the increase of P serum levels in the individual patient, even within the normal range, may occur quite early in the course of CKD (as little as 50 mL/minute of glomerular filtration rate), accompanied by the increase in PTH (parathyroid hormone) and even earlier by the increase of FGF23 (fibroblastic growth factor 23). Following a dietary intake of P, from the very early stages of CKD, FGF23 causes a phosphaturic response contributing to maintenance of a neutral P balance (Baylan et al., 2006).

Based on observational studies in hemodialysis (HD) patients, it has been suggested that hyperphosphatemia are associated with cardiovascular (CV) morbidity (eg, mitral annular calcification, peripheral arterial calcification, and increased carotid intima-media thickness [cIMT]). Moreover, control of hyperphosphatemia may have a myocardial protective role (Eduardo Lacson et al., 2015).

In the current study, we studied the effect of Haemodiafiltration on the CKD-MBD in regular haemodialysis patients with measures of ckd-mbd in chronic renal faliure patients undergoing heamodilysis.

In our study, we studied 100 patients divided into 2 groups.

- Group (1) included 60 patient were on heamodilysis.
- Group (2) included 40 patient were on haemodiafiltration.

Overall, there were 48 male and 51 female and the age was 49 (41 - 59), 51.2 % had hypertension (n=21) in HDF and 63.8 % (n=37) in HD, 14.6 % were diabetic (n=6) in HDF and 27.6 % (n=16) in HD, 24.4 % were HCV positive (n=10) in HDF and 17.2 % (n=10) in HD.

Okada et al. (2007), demonstrated that Increase in intact PTH correlates significantly with decline in Residual kidney Function after adjustment in other variables such as serum Ca, phosphate, and creatinine.

In our study, we found a highly statistical significant difference (P value <0.001) between 2 groups regarding the mean of (PTH). By comparison between the two groups we found a significant difference in The level of Parathyroid Hormone as a high level of PTH with HD (mean 420-786) in comparison with HDF (mean150-350) (p value<0.001).

By comparison between the two groups we found a significant difference in The level of S. Phosphrus as a high level of Po4 with HD (mean 5.2 ± 0.77) in comparison with HDF (mean 3.83 ± 0.0.41).

These results go in agreement with the results reported by (Kestenbaum et al., 2005) who applied that there was statistically significant relationship between Serum Phosphate Levels and Mortality Risk among People with Chronic Kidney Disease.

Elevated serum phosphate levels have been linked with vascular calcification and mortality among dialysis patients.

Serum phosphate levels >3.5 mg/dl were associated with a significantly increased risk for death. Mortality risk increased linearly with each subsequent 0.5-mg/dl increase in serum phosphate levels (Kestenbaum et al., 2005). Elevated serum phosphate levels were independently associated with increased mortality risk among this population of patients with CKD. (Kestenbaum et al., 2005).

Our Study revealed the major role of HDF in chronic kidney disease–mineral and bone disorder (CKD–MBD) management.

Because there is a chief problem that Hemodialytic removal of phosphrus does not equal the high P intake linked to the high dietary protein requirement of dialysis patients but HDF can overcome this problem by Using a mixed diffusive–convective hemodialysis techniques.

The intradialytic output kinetics of P are completely different from that of urea or other small molecules for the different body volume distributions because Phosphate kinetics during HD increased hydrated radius of “P “ renders the passage through the pores of the dialysis membrane more difficult.

So Our Study prove that there is a great effect of HDF on bone mineral diseases and this effect go in agreement with many studies that encourage use of HDF for CKD-MBD patients.

There are many studies could be attributed for explanation this effect and the only possible explanation which may be responsible up till now is that Albumin loss is dependent only on dialyzer type and TMP applied and Albumin molecules squeeze through pores with high TMP.

These results go in agreement with our results reported by who stated that there statistically significant relationship between Albumin loss and HDF in comparison with HD.

In our study, we found a highly statistical significant difference (P value <0.000) between 2 groups regarding the mean of (S. Albumin).

By comparison between the two groups we found a significant difference in the level of Albumin as the level of Albumin with HDF (mean 3.36 ± 0.21) in comparison with HD (mean 3.39 ± 0.21).

Another Study which agree with the same results show that Transmembrane pressure modulation in

high-volume mixed HDF may help to Optimization efficiency and minimize protein loss (LA Pedrini and G cozzi, 2017) and this study depend on different Blood flow rate.

In our study, we found no significant difference between 2 groups regarding the mean of (Hematocrite).

But Another Study which disagree this report and it revealed that increasing Hematocrite in group of HDF in comparison with HD and they denoted this effect to high TMP and Post-dilution module of HDF. (Plasma water, Hematocrit and protein changes during HDF).

As we know that Middle molecules, consisting mostly of peptides and small proteins with molecular weight the range of (500-60,000) Da, accumulate in renal failure and contribute to the uraemic toxic state. B2-Microglobulin (B2-MG) with a molecular weight of 11,000 is considered representative of these middle molecules. This convective component of high-flux dialysis can be enhanced in a predictable way by haemodiafiltration (HDF). (Ronco C and Aljama P, 2007).

In our study, we found a highly statistical significant difference (P value <0.001) between 2 groups regarding the mean of B2 Microglobulin.

By comparison between the two groups we found a significant difference in the level of B2 Microglobulin as a high level of with HD (mean 303 ± 256 - 589) VS (mean 34 – 125) in HDF.

This important item go in agreement with another study in (Department of Nephrology, Chang Gung Memorial Hospital, Taipei, Taiwan) that revealed an inverse correlation between the β_2-microglobulin level and the duration of HDF, if patients were treated for more than 12 months ($p = 0.031$) and concluded that On-line HDF has an increased dialysis efficiency compared to high-flux dialysis.

So Long-term HDF further reduced β_2-microglobulin levels, thus, it may provide an improved modality for renal replacement therapy.

The Japanese Society for Dialysis Therapy found that First-time CTS Carpal Tunnel Syndrome almost doubled with every 5-year increase in dialysis vintage. So CTS were highest for patients aged 60-70. Other factors associated with CTS were gender, serum albumin, and diabetic nephropathy. β_2 MG clearance >80% may decrease the incidence of CTS.

As the percent reduction of B2microglobulin with HDF was better than in the HD mode, as has been previously reported. This in itself may carry considerable significance as dialysis related amyloidosis has become a major problem in our aging dialysis population. If a particular dialysis mode were associated with a genuine lower incidence of dialysis related amyloidosis then it would be welcomed.

However, some studies disagree this explanation at present, because the more occurrence of lower post-dialysis B2m levels (and certainly not normal levels) is not sufficient evidence to suggest this. But It has recently been reported that the generation rate of B2m is the same in those with renal failure and those with normal renal function (Floege J and Granolleras, 2008). A previous report also demonstrate a fall in pre-dialysis 2m levels over a five year period of HDF. Pre-dialysis B2m levels have been reported to fall with ongoing HDF in two studies but follow-up periods have been short (6 and 12 months) (Mayer and Thum J, 2011). It has been further reported that HDF using large volumes of infusate (60 liters) is also associated with a gradual decrease in pre-dialysis B2m levels.

Despite this, It is therefore obvious that the augmented clearance of B-2m by HDF using highly permeable polysulfone membranes and using convective component of HDF adds more to the clearance of B2m; this provides a lower time averaged concentration of B2m than in HD thus reducing the risk exposure time for B2m related pathology.

So we encourage Long-term HDF which may provide an Optimum modality as renal replacement therapy for prevention of Carpal Tunnel Syndrome, It is still unknown, however, whether HDF can clinically reduce the incidence of dialysis related amyloidosis.

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