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Comparison between the Effects of High-Flux and Low-Flux Membrane on Hemodialysis Adequacy

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Abstract

Background: Hemodialysis (HD) therapy is the most commonly used modality of renal replacement therapy worldwide to treat patients with end stage renal disease (ESRD). The principle of hemodialysis depends on diffusion of solutes between the patient's blood and the dialysate fluid through a semipermeable membrane. Two types of such membranes are found in regard to pores sizes: low-flux membrane and high-flux membrane. The HD adequacy can be assessed by measuring the urea reduction ratio (URR) and the Kt/V.

Aim: To determine whether there is effect on the hemodialysis adequacy when a high-flux membrane is used instead of the low flux membrane.

Methods: this is a cross sectional study. The URR and Kt/V were measured for 27 HD patients in two occasions, one on high-flux and the other on low-flux membrane and the results were compared statistically.

Results: The high-flux membrane was associated with statistically significant higher URR and Kt/V (p=0.02 and 0.008 respectively).

Conclusion: High-flux membrane is associated with better dialysis adequacy than low-flux type in HD.

Keywords: Hemodialysis; High-Flux Membrane; Low-Flux Membrane

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Introduction

Renal impairment may be either acute "acute kidney injury" (AKI) or chronic "Chronic kidney disease" (CKD). AKI is an abrupt and usually reversible decrease in kidney function. The definition of AKI is based on specific criteria that have been sequentially developed. The Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging system is the most recently designed. CKD is defined as estimated glomerular filtration rate [eGFR] (<60 mL/min/1.73 m^2) and/or the presence of features of kidney damage (e.g. urine albuminuria/creatinine >30 mg/g or urine sediment abnormalities) for at least 3 months. CKD can be classified according to its cause into systemic or primarily renal, eGFR (G stages) into five stages, the last of which is end-stage renal disease (ESRD) and level of albuminuria (A stages) into three stages: normal, moderately increased, and severely increased albuminuria. The risk of CKD progression is inversely linked to eGFR and directly to the amount of albuminuria [1-4]. Management of chronic kidney disease involves treatment of its reversible causes, preventing or slowing its progression, treatment of its complications, adjusting drug doses when appropriate for the level of (eGFR) and identification and adequate preparation of the patient in whom renal replacement therapy(RRT) will be required. To decrease morbidity and mortality; patients with CKD should be referred to a nephrologist when (eGFR) is <30 mL/min/1.73 m^2 in order to discuss and potentially plan for RRT which includes peritoneal dialysis (PD), Hemofiltration (HF), Hemodialysis (HD), Hemodiafiltration (HDF) and Renal transplantation [5,6]. There are many clinical indications to initiate dialysis in patients with CKD like persistent nausea and vomiting, pericarditis or pleuritis, uremic encephalopathy or neuropathy, bleeding diathesis and refractory fluid overload, hypertension or metabolic disturbances [7-9].

Principle of HD

HD is the main modality of RRT that is used worldwide, as it may be used for AKI, CKD or in some cases of poisoning. It implies gaining access to patient's blood through arteriovenous fistula, arteriovenous graft or double lumen catheter placed in a central vein. The blood is then circulated through tubing system using a special pump that direct the blood to enter through a large number of capillaries bundled together in a dialyzer. The capillaries are made up of semisynthetic materials that are biocompatible. These constitute membranes that are semipermeable and are capable of allowing exchange of small molecules under the effect of the concentration gradient (diffusion) with the dialysate which is a solution that is passing through outside the capillaries and usually in the opposite direction relative to the blood, and this solution contains sodium chloride, bicarbonate, and varying concentrations of potassium. Diffusion through the membrane allows low molecular-weight substances such as urea, potassium, and organic acids to move across according to the concentration gradient. Excess body fluid is removed by ultrafiltration, which is achieved by applying trans membrane hydrostatic pressure across the dialyzer. HD offers the best rate of small solute clearance in AKI, as compared with other techniques such as hemofiltration. HD is usually carried out for 3–5 hours thrice weekly, either at home or in an outpatient dialysis unit. The intensity and frequency of dialysis should be adjusted to achieve a URR of over 65%. More frequent dialysis and nocturnal dialysis can achieve better fluid balance and electrolyte control than standard dialysis and, in particular, better control of serum phosphate levels. The degree of diffusive transport is a function of the concentration difference of the solute across the membrane, membrane surface area, porosity and thickness of the membrane, molecular size of the solute and flow rate of blood (Qb) and dialysate (Qd) [10-14].

Dialyzers and Membranes

Dialyzers are composed of a polyurethane capsule or shell within which the membranes are contained in one of two ways featuring the types of the dialyzers:

Hollow-fiber (capillary) dialyzers-which are the most common dialyzers in current use. They contain thousands of hollow fibers each similar in structure to a human capillary.

Parallel-plate dialyzers which are flat sheets of membrane material arranged in parallel. These are no longer in common use. In any type of the dialyzers the substances flows across these semipermeable membranes from one side to other [15,16]. Membranes are classified according to the material, and the porosity. According to the material, they could be:

- Natural unmodified cellulosic membranes derived from cotton .They activate complement and leukocytes, inducing an inflammatory reaction and are regarded as "bioincompatibile". Example of this type is Cuprophane filter.

- Modified/regenerated cellulosic membranes (semisynthetic): natural cellulosic membranes are modified chemically to reduce or mitigate the immunological response and so, being more 'biocompatible' than the unmodified membranes. Example of this type is Hemophane filter.

- Synthetic membranes are regarded as being more "biocompatible" in that they incite less immune response than unmodified/ modified cellulose-based membranes. Example of this type is Polyflux filter which is made of polyamide and is the type used in this study [17-19].

While the materials of the membrane are affecting the 'biocompatibility', the porosity and so the degree of the 'flux' of the membrane will affect the clearance of the solutes. There are two available types of membranes in regard to size of pores:

- Those with small pore size, known as 'low-flux' membranes, allow clearance of molecules smaller than 500 Daltons into the dialysate (such as the urea and creatinine). Larger molecules are not removed from the body by the low-flux membranes, and are responsible of bad outcome as the increased inflammatory status and amyloidosis that is caused by accumulated β2 microglobulin and other moderate sized molecules.

- High-flux membranes with larger pore sizes have been developed to allow greater clearances of moderate-sized molecules up to 15000 Dalton, including many of the inflammatory proteins, the amyloidogenic $ß_2$ microglobulin, advanced glycation end products, and lipoproteins [20-22]. High-flux dialysis may have a number of long-term benefits, including Lower incidence of β2 microglobulin-related amyloidosis, improved lipid abnormalities and lower cardiovascular mortality [19,23,24].

Hemodialysis Adequacy

The 'dialysis dose' describes the percentage of removal of a particular solute from the patient's body during a dialysis session, giving us an idea about dialysis adequacy as this can impact morbidity and mortality. Two methods are widely used:

- Extraction ratio: the ratio by which a solute is decreased as a result of dialysis, the urea is often chosen (so called urea reduction ratio (URR)).

- Kt/V is another method to assess the dialysis dose, 'K' stands for the blood flow rate of the dialyzer (mL/min), 't' for time of the dialysis session (min), and 'V' for volume of water a patient's body contains [9,10,25-28]. Current guidelines in the United States target a URR of at least 65% or a Kt/V of at least 1.20 as markers of adequate dialysis [29].

Some factors that affect the delivered dialysis dose are modifiable and include: effective duration of dialysis, Qb, Qd, and dialyzer effective membrane surface area. Theoretically speaking; increasing the duration of dialysis, Qb, Qd, and/or the membrane surface area would enhance the adequacy of HD, but practically, these interventions, are either not significant or not feasible. For example, increasing the duration of the dialysis over four hours is beyond the patient's tolerance and will increase the cost of dialysis to a large extent. Also, increasing the dialysate flow rate does not have a significant effect on the adequacy of the dialysis. Furthermore, increasing blood flow beyond the specified range can be associated with some complications such as hypotension, hemolysis, and muscular cramps that may lead to intolerance of continuous dialysis. Currently, there are little studies that compare the effects of the type of membrane-according to porosity, on the dialysis adequacy [11,30-32]. Aim of the study: This study aims to determine whether there is a beneficial effect on the hemodialysis adequacy when a high-flux membrane is used instead of the low flux membrane.

Methods

Twenty seven patients with ESRD on maintenance HD who are already utilizing the high-flux membrane in Al-Hakeem dialysis center were included in the study. The comparison between the two membranes (i.e. the high and low-flux) was observed in the same group in two occasions; the first one while they were using their usual membrane (the high-flux)-as assigned by their nephrologist; and, the second occasion, while they were temporarily switched to low flux-membrane for about 40 days because of the shortage of some materials (including the high-flux membrane dialyzers) that occurred at the end of 2018.

Inclusion Criteria

We included all patients on high-flux membrane maintenance HD in Al-Hakeem dialysis center in Najaf governorate in Iraq.

Exclusion Criteria

Those with hemodynamic instability during the dialysis that frequently causing interruption of the session. **Interventions and Comparison**

The study was accomplished during November and December 2018 in Al-Hakeem dialysis center. Demographic data, of the selected group, including gender; age; duration being on hemodialysis and type of vascular access were recorded. During both occasions (first; while on high-flux membrane as their usual type of membrane; and the second one while were temporarily switched to low-flux type), pre-dialysis and post-dialysis urea (in mg/dL) had been measured. The first blood sample (pre-dialysis urea) had been taken from the pre-dialyzer arterial line at the onset of the session. The second sample (post-dialysis urea), was taken from the same site after reducing the blood flow rate down to a 100 ml/min for about 30 seconds before ending the session. Information of the dialysis session, including the duration (in hrs.,); the ultra-filtrate (UF) (in liters); and the post-dialysis weight (in Kg), had been recorded.

The URR had been obtained using the following equation:

- URR= (predialysis urea - postdialysis urea) / predialysis urea x 100 % [10]

And the Kt/V-using the Daugirdas formula had been calculated as follow:

- Kt/V = [(post-dialysis urea/pre-dialysis urea) - (0.008 × t)] + [4 - (3.5 × postdialysis urea/pre-dialysis urea) × UF/postdialysis weight [10,33]

The hemodialysis machines are of AK 200 Ultra S 2014 version, made by Gambro Company, Sweden. Regarding the filters used, both types (high- and low-flux) are of Polyflux type (made from polyamide, a synthetic polymer) manufactured by the same company (Gambro, Sweden). Both types of membranes used in the study (whether high- or low flux) were of two sizes; either ($1.7m^2$ or $2.1m^2$). Also, it is important to mention that patients were dialyzed against the same filter size, Qb, Qd, and duration of dialysis during both stages of the study. Specifications of high-flux and low flux membranes used in the study are shown in the table (Table 1). The urea had been measured by an enzymatic colorimetric test, using HumaLyzer 2000 machine, a product of HUMAN co., Germany. The kit used (Urea liquicolor, REF/10505) was made by the same company (HUMAN co., Germany,).

Ethical Issues

The participants had been clearly informed verbally about the study as being completely observational rather than a clinical trial because we exploited the period of shortage of high-flux membrane supply and did not change the membranes for the purpose of the study. Demographical information plus other data had been taken noninvasively except for the two blood samples taken pre and post-dialysis that actually are routinely done monthly to all patients on HD "as a policy" in Al-Hakeem hospital dialysis center.

Statistical Analysis

Data were analyzed by using the 22 version of SSPS (IBM Corporation). Both descriptive (mean, standard deviation, and percentage) and inferential (T test and paired t-test) statistical analyses were used. P value of less than 0.05 was taken as statistically significant.

Results

This cross-sectional observational study enrolled 27 patients, 15 of them (55.5 %) were males and 12 (44.5 %) were females, with the mean age of [47.18 ± 16.07] years old. All of them are on maintenance dialysis for a mean of [4.66 ± 2.62] year's duration. Only one of them was using arteriovenous graft, while all the others were using arteriovenous fistulas as a vascular access for HD. The difference between the means of the pre-dialysis urea of the high-flux and low flux membranes was not statistically significant (P value > 0.05). Also, regarding the means of the post-dialysis urea of both types were not significantly different (P value > 0.05) (Table 2).

The mean of URR for the patients with high-flux membrane was 66.75 % ± 8.23%, which was higher than the URR on low-flux membrane [(60.76 ± 10.93)%] and this difference was statistically significant ($p < 0.05$). Moreover; the obtained Kt/V of the patients while on the high-flux membrane (mean 1.36 ± 0.30), is higher than when on low-flux membrane (mean 1.13 ± 0.31). This difference is statistically significant ($p < 0.05$) (Table 3).

The URR achieved the required target in 70.3% of the patients while on high-flux membrane; while this was observed only in 30% on low-flux membrane. In the same way; the required target of Kt/V was achieved in 74 % of patients with the high-flux membrane, and only in

Table 1: Specifications of low-flux and high-flux filters*.

	Low-flux filter		**High-flux filter**	
Effective membrane area (m^2)	1.7	2.1	1.7	2.1
UF coefficient** in vitro [ml/(h*mmHg)]	12.5	15	70	85
Max. transmembrane pressure (TMP) (mmHg)	600	600	600	600
Range of blood flow rate (Qb) (ml/min)	200-500	300-500	250-500	300-500
Range of dialysate flow rate (Qd) (ml/min)	500-800	500-800	500-800	500-800

(*): Data were taken from the brochure provided by the company.
(**): The ultrafiltration coefficient (K_{Uf}) is the volume of fluid (in mL/hr) that is transferred across the membrane per mmHg of pressure and it is a measure of a dialyzer's permeability relative to water, so the K_{Uf} differs between membranes according to pore size (flux) [11].

Table 2: Comparison of mean URR and mean Kt/V in high flux and low flux membranes.

	Low-flux	**High-flux**	**P value**
Mean URR	60.76(± 10.93)%*	66.75 (± 8.23)%*	0.02
Mean Kt/V	1.13 ± 0.31*	1.36 ± 0.30*	0.008

(*): mean ± SD

Table 3: Comparison of percentage of patients on low-flux and high-flux membranes that reached target URR and Kt/V*.

Type of Membrane	**Target URR**	**Target KT/V**
High-flux	70.3 %	74 %
Low-flux	30 %	51.8 %

(*): Data were expressed as % of the total number dialyzed by the same membrane.

51.8 % of them while on the low-flux type (Table 4).

Discussion

The sample size of the current study (27 patients) represents all the patients that are on high-flux membrane HD in Al-Hakeem center after excluding only two patients (they were known to have hemodynamic instability with frequent interruptions of HD sessions). This sample size was approximate to some studies as Haghighi MJ, et al. (2016) (22 patients), Shahdadi H, et al. (2017) (22 patients), and Oshvandi K, et al. (2014) (40 patients). The sex ratios of the participants as well as their mean age were also approximate with data of those studies [34-36]. Both pre-dialysis and post-dialysis urea levels were not significantly different in both stages. These findings were consistent with the above mentioned studies [36,37]. The present study results showed; that the high-flux membrane was associated with higher URR as compared to the low-flux type and this difference was statistically significant (P value 0.02). Also; the Kt/V was higher in high-flux type than the low-flux one and it was also statistically significant (P value 0.008). So the high-flux membrane is associated with higher dialysis dose and so, with better dialysis adequacy. El Arbagy AR, et al. (2014) conducted a study that included 40 patients who were on maintenance HD for at least 6 months duration, all of them were already utilizing low-flux membrane. During that study, the patients were switched to high-flux membrane, and a comparison were done between high-flux and low-flux membranes in regard to effect on blood urea, serum creatinine, some electrolytes, and PTH. That study showed that the high-flux membrane was more effective in removal of uremic toxins and decreasing metabolic complications than the low-flux membrane [38]; although, they did not investigate the effect of the flux type on URR and Kt/V. Shahdadi H, et al. (2017) conducted a study that included 22 patients and investigated the effect of increasing Qb and using of high-flux membrane. That study revealed significant increase in Kt/V when the patients were switched to high-flux membrane-without changing the Qb (p=0.006) [35]. Regarding the significance of using high-flux membrane in that study, it was similar to the results of the current study, but they use only the Kt/V for comparison and only 22 patients were included. Haghighi MJ, et al. (2016) included 22 patients in a study and compare the Kt/V between low and high flux dialyzers. That study showed that the high-flux membrane was associated with higher adequacy with a statistical significance (p=0.006) that was consistent with the results of the current study regarding the effect on Kt/V, but they did not take the effect on URR into account. Narimani R, et al. (2015) accomplished a study that investigated the effect of membrane type on dialysis adequacy when larger volumes (>3 liters) are ultra-filtrated. That study revealed that high-flux membrane was associated with higher Kt/V than the low-flux type did, this was statistically significant (p=0.01). Again, this study did not investigate the effect on URR although the results were consistent with the present study regarding the effect on Kt/V. They found no significant effect of high-flux membrane on Kt/V when less than 3 liters of fluid were ultra-filtrated [39]. Oshvandi K, et al. (2014) performed a study in which 40 patients were included and a comparison of URR and Kt/V between two stages was done, first on low-flux membrane and the second one on high-flux membrane. The results showed that the URR and the Kt/V were better increased with the high-flux membrane. While the increase in Kt/V was statistically significant (p=0.01), the difference in URR between the two types of membranes was not statistically significant (p=0.21) [37].

El Arbagy AR, et al. (2014) included 80 patients in a study that investigated the effect of membrane type on both URR and Kt/V. That study revealed that the high-flux membrane was associated with higher Kt/V and URR. The difference in Kt/V was statistically significant (p=0.01), that was consistent with the current study, but the URR difference was not significant (p=0.22) and so inconsistent with our results [38]. These differences with the last two studies might be attributed to various factors including the larger sample size, and the difference in the brand and model of the used dialysis machines and filters. The current study showed that dialyzing against the high-flux membrane had the best ratios of reaching the targets of both URR and Kt/V. It is worthy to mention that the URR is somewhat imprecise way to assess the HD adequacy because it doesn't involve the urea generation during the dialysis session and also the urea removed by the ultrafiltration (through convection) but yet it is still used widely. The Kt/V that is used in the current study (the Daugirdas formula) is more precise than the URR in regards to these two issues. Yet, this type of Kt/V doesn't take into account the urea that would be redistributed from extravascular compartment into the intravascular one that is usually taking about 30-60 min after the dialysis (this is responsible for the post-dialysis urea rebound) and it only consider the urea in one compartment (intravascular) and hence called as single-pool Kt/V (spKt/V). Another type of Kt/V is called the equilibrated Kt/V (eKt/V) is regarded even more accurate than the spKt/V because it considers all the compartments (rebound urea) but is difficult to apply because it is beyond the patient's tolerance to wait for about an 'extra' hour for the blood sampling in addition to the extra load on the staff and space [10, 11, and 40].

Conclusion

The use of high-flux membrane is associated with better dialysis adequacy than the low-flux type in HD.

Recommendations

Using the high-flux membrane is recommended for better dialysis adequacy. Further studies that include the eKt/V that would be with fewer biases are suggested.

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