

## High Flux Versus Low Flux Dialysis: Impact on Intradialytic Hypertension and Adequacy of Dialysis

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### ABSTRACT

**Background:** Intradialytic hypertension is an underrecognized complication in hemodialysis patients, increasing cardiovascular morbidity, mortality, and hospitalization.

**Objective:** The aim of the current work was to detect the incidence of intradialytic hypertension in hemodialysis patients and to compare the effect of high flux versus low flux dialysis on intradialytic hypertension and adequacy of dialysis.

**Patients and Methods:** The study was conducted on 200 patients on regular hemodialysis in Beheira governorate. The patients were divided into: **Group 1** including 100 patients on hemodialysis with high flux dialyzers and **Group 2** including 100 patients on hemodialysis with low flux dialyzers.

**Results:** The incidence of intradialytic hypertension in hemodialysis patients was 23.5 % at the start, 21% after one month and 13% after three months duration. There was a significant reduction in number of intradialytic hypertension patients after one month duration and after three months in both groups. Adequacy of dialysis in the form of Kt/V and urea reduction ratio showed highly significant improvement by the end of the study in the high flux group. Kidney function tests, serum parathyroid hormone levels and serum hemoglobin levels showed significant improvement at the end of the study in high flux group compared to low flux group.

**Conclusion:** It could be concluded that the current study has not demonstrated a significant difference between both groups regarding the effect on intradialytic hypertension, but adequacy of dialysis in the form of Kt/V and urea reduction ratio improved significantly by the end of our study in the high flux group.

**Keywords:** Intradialytic hypertension, Hemodialysis, High/low flux dialysis

### INTRODUCTION

In newly diagnosed patients with end stage renal disease (ESRD), more than 85% of them present with hypertension (HTN). HTN in those patients is multifactorial. Elevated peripheral vascular resistance and persistent hypervolemia are important contributing factors. In patients maintained on 3 HD sessions per week, blood pressure (BP) rises during the hemodialysis (HD) session, especially in older patients and those with higher dry weight. The main goal of HD is to control the extracellular volume (ECV), as inadequate sodium and fluid removal leads to fluid overload, HTN and higher mortality rates<sup>(1)</sup>.

It is well-known that HTN is associated with abnormalities in cardiac structure and function including diastolic dysfunction, left ventricular hypertrophy, and arterial stiffness. BP shows dynamic changes during HD sessions including both intradialytic hypotension and HTN, which are 2 special situations significantly increasing the risk of mortality in those patients. It was found that intradialytic hypertension (IDH) was associated with a higher mortality risk than intradialytic hypotension<sup>(1)</sup>.

During the HD session, a reduction in systolic BP of about 10-15 mm Hg is expected with BP decreasing steeply during the first hour and then decreasing more slowly during the remaining hours of the session. However, some patients experience rises in BP during HD sessions. As BP readings vary frequently both during and between HD sessions in most ESRD patients, it is better to observe BP patterns over

prolonged periods of time to identify patients who experience IDH most frequently<sup>(2)</sup>.

No standard definition of IDH exists but has most commonly been defined as  $\geq 10$  mmHg rise in systolic blood pressure (SBP) during dialysis. IDH (intradialytic SBP rise  $\geq 10$  mmHg at  $\geq 4$  over six consecutive sessions) is estimated at 5–15% of HD patients and is associated with poor prognosis<sup>(3)</sup>. IDH has been associated with higher ambulatory BP, increased cardiovascular morbidity and mortality, and frequent hospitalizations in HD patients<sup>(4)</sup>.

IDH has been associated with higher risk for both short-term (6 months) and long-term (2 years) morbidity and mortality. It is still unclear if IDH can be considered a marker for modifiable risk factors known to affect cardiovascular morbidity and mortality<sup>(5)</sup>. Although clinically significant, little is known about the pathophysiological mechanisms underlying IDH<sup>(6)</sup>.

Proposed pathophysiological mechanisms leading to IDH are volume overload, stimulation of renin angiotensin system, activation of sympathetic nervous system together with the effects of vasoactive peptides, increased hematocrit levels with ultrafiltration, changes in electrolyte levels during HD and removal of antihypertensive medications<sup>(7)</sup>.

Some studies stated that IDH may be due to an impaired endothelial cell (EC) response to HD, with more increases in plasma endothelin-1 (ET-1) relative to nitric oxide, together with impaired flow-mediated vasodilation (FMD)<sup>(8)</sup>.

It is not fully understood how IDH can lead to adverse cardiovascular outcomes. It is apparent that

IDH, directly or indirectly may lead to left ventricular hypertrophy, a known risk factor for adverse cardiovascular events in HD patients. Recently, observational study performed on 100000 HD patients showed that any increase in systolic BP during dialysis sessions was associated with increased mortality, ensuring the importance of IDH<sup>(4)</sup>.

Post-dialysis volume expansion of extracellular water (ECW) and intravascular compartments measured by the combination of bioelectrical impedance and echocardiography in patients on maintenance HD is an important factor for the development of IDH<sup>(9)</sup>.

Management of IDH should include an initial reassessment of the dry weight of HD patients. It is advisable to treat persistent IDH with less dialyzable antihypertensive drugs. Also, some studies stated that carvedilol may add a specific benefit. Both nebivolol and irbesartan were found to decrease post-dialysis and 24-hours BP in IDH patients and nebivolol was somehow more potent than irbesartan<sup>(3)</sup>. Adjustment of the dialysate sodium can help, with careful monitoring of electrolytes and hemodynamics<sup>(2)</sup>.

It is reported that nearly 40% of patients with ESRD die because of cardiovascular disease. Cardiovascular disease is also a major challenge in renal transplantation. A major factor leading to cardiovascular disease in HD patients is vascular calcification which causes vascular stiffness, higher pulse wave velocities, and elevated pulse pressures. Vascular calcification is thought to be caused by abnormal regulation of phosphorus and calcium and disruption of mineral metabolism. High flux hemodialysis (HFHD) is superior to low flux hemodialysis (LFHD) in treating anemia and improving nutritional status. Also, HFHD can better decrease FGF-23, correct calcium and phosphorous metabolic disorder and improve micro-inflammatory state<sup>(10,11)</sup>.

Ensuring the tolerability of HD patients for high-flux high-efficiency HD results in an increase in dialysate sodium prescriptions from 120 to  $\geq 140$  mEq/L. High dialysate sodium concentration may lead to more interdialytic weight gain, which contributes to HTN<sup>(12)</sup>.

The aim of the current study was to detect the incidence of IDH in HD patients in Beheira governorate and to compare the effect of high flux versus low flux dialysis on both; IDH and adequacy of dialysis.

## PATIENTS AND METHODS

This prospective cohort study was conducted on 200 patients on maintenance HD from different HD units in Beheira governorate.

After detecting the incidence of IDH, all 200 patients were divided into two groups: **Group 1:** 100 patients on HD with high flux dialyzers and **Group 2:** 100 patients on HD with low flux dialyzers.

The study included patients with ages 18 years or more with HD vintage > 6 months. Achievement of estimated dry weight was deemed by their primary

nephrologist to be at their target dry weight based on recent challenge of dry weight and the absence of clinical symptoms of volume overload. Patients were on HD sessions thrice weekly, four hours for each session using the same bicarbonate dialysate concentration, and heparin as anticoagulant, blood pump was 250- 300 ml/min for all patients. All patients were receiving the same erythropoietin type but with different doses according to monthly hemoglobin level. Patients with active neoplasm or active wounds or change in dialysis modality during study period were excluded from the study.

All patients were subjected to history taking with full and detailed history including (age, etiology of ESRD, duration of HD, type of vascular access and types of antihypertensive drugs used). Complete clinical examination was done including BP measurement by sphygmomanometer before HD session, every hour throughout the session and immediately after session to detect the presence of **IDH**, which is defined as (intradialytic SBP rise  $\geq 10$  mmHg at  $\geq 4$  over six consecutive sessions).

We compared the effect of high flux versus low flux dialysis on IDH in these patients after one month and three months and the incidence of IDH was reviewed.

**Investigations:** were done at the start of the study and at the end with comparison between both groups. CBC, and serum BUN, creatinine, sodium, potassium, PTH, calcium, phosphorus, cholesterol, triglycerides were measured.

**Adequacy of dialysis** was estimated at the start and at the end of the study by

### Calculating Kt/V using Kt/V Daugirdas Formula:

$$\text{Kt/V Daugirdas} = -\ln((\text{BUNPost} / \text{BUNPre}) - (0.008 * \text{Hours})) + ((4 - (3.5 * \text{BUNPost} / \text{BUNPre})) * \text{UFVol} / \text{WeightPost})^{(13)}$$

### Calculated Urea reduction ratio (URR):

$$\text{URR} = 100\% \times (\text{predialysis BUN} - \text{postdialysis BUN}) / \text{predialysis BUN}^{(14)}$$

### Ethical Considerations:

The study was approved by the local Ethical Committee of Ain Shams University. An informed consent was obtained from all patients before enrolment in the study after explaining the study purpose, methods, risks and benefits to them. The individuals involved in the research had the right to withdraw from the study at any time without jeopardizing their right to receive their medical care. All data collected will remain confidential and will be used for the research purpose only. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

**Statistical Analysis:**

Data were analyzed using the Statistical Package for the Social Sciences for Windows version 16.0 (SPSS Inc., USA.). Description of data was in the form of mean (M) and standard deviation (SD) for quantitative variables and by frequency and percentage for qualitative variables. Spearman correlation test (r) studied the relationship of quantitative variables. Significance levels measured according to P value (probability) with P>0.05 insignificant, P<0.05 significant, P<0.01 highly significant.

**RESULTS**

The mean age of the study population was 59 (+/- 6.4) and it was matched between both groups. There was no statistically significant difference as regards sex (P value 0.887).

The incidence of IDH in HD patients in Beheira governorate was 23.5% at the start, 21% after one month and 13% after three months duration. The incidence of IDH in high-flux dialysis patients was 21.0% vs 26.0% in low-flux dialysis with no statistically significant difference (P> 0.05). There were no statistically significant differences between both groups as regards effect of high-flux vs low-flux dialysis on IDH after one month and at the end of the study (P> 0.05). There were significant differences between the three studied periods in each group (p ≤ 0.05), as the number of IDH patients decreased after one month duration and after three months in both groups, as shown in **table 1**.

**Table (1): Comparison between the studied groups according to the effect of type of dialyzer on IDH**

| IDH                                      | High flux<br>(n = 100) |      | Low flux<br>(n = 100) |      | χ <sup>2</sup> | p     |
|------------------------------------------|------------------------|------|-----------------------|------|----------------|-------|
|                                          | No.                    | %    | No.                   | %    |                |       |
| At the start of the study                | 21                     | 21.0 | 26                    | 26.0 | 0.695          | 0.404 |
| After 1 month                            | 18                     | 18.0 | 24                    | 24.0 | 1.085          | 0.298 |
| After 3 months (at the end of the study) | 10                     | 10.0 | 16                    | 16.0 | 1.592          | 0.207 |
| p <sub>1</sub>                           | 0.002*                 |      | 0.009*                |      |                |       |

**IDH:** Intradialytic hypertension.

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

\*: Chi-square test; •: Independent t-test.

There were no significant differences between both groups as regards to the etiology of ESRD, HD duration, type of vascular access and anti-hypertensive drugs used (P >0.05). There was no statistically significant difference between both groups as regards to hemoglobin levels at the start and at the end of the study (P>0.05). There was no statistically significant difference between both groups as regards to pre – dialysis BUN or creatinine levels at the start of the study (P > 0.05), while there were significant differences between both groups as regards pre – dialysis BUN at the end of the study, post – dialysis BUN at the start and at the end of the study and creatinine levels at the end of the study with **P value (0.001), (<0.001), (<0.001) and (0.002)** respectively.

In our study, there were no significant differences between both groups as regards to serum Na, K and Ca levels at the start and at the end of the study (P < 0.05), while there was significant difference between both groups as regards to serum Po<sub>4</sub> levels at the end of the study with (**P value 0.034**). Intact parathyroid hormone (IPTH) levels at the start and at the end of the study showed no significant difference between both groups (P > 0.05). Cholesterol levels at the start and at the end of the study and serum triglycerides levels at the start of the study showed no significant difference between both groups (P> 0.05), while there was a significant difference between both groups regarding serum triglycerides levels at the end of the study with (**P value 0.042**).

There were no significant differences between both groups as regards Echo findings (P value 0.473). There was highly significant improvement at the end of the study in high flux group, in the form of reductions in all of pre-dialysis BUN, serum creatinine, serum po<sub>4</sub> and IPTH levels with **P value <0.001**. Also, post-dialysis BUN levels showed significant reduction at the end of the study with **P value 0.002**, as shown in **table 2**. Finally, serum hemoglobin levels were better at the end of the study with **P value 0.021**.

**Table (2): Laboratory markers at the start and at the end of the study in High flux patients:**

|                     | At the start<br>Mean ± SD. | At the end<br>Mean ± SD. | Test of sig. | p       |
|---------------------|----------------------------|--------------------------|--------------|---------|
| Hemoglobin (g/dL)   | 9.49 ± 2.04                | 9.85 ± 1.61              | t=2.348*     | 0.021*  |
| Pre - dialysis BUN  | 65.56 ± 12.51              | 61.01 ± 13.43            | t=5.304*     | <0.001* |
| Post - dialysis BUN | 27.72 ± 6.34               | 24.60 ± 5.18             | t=3.232*     | 0.002*  |
| Creatinine (mg)     | 9.67 ± 2.70                | 8.82 ± 2.07              | t=5.642*     | <0.001* |
| Po4 (mmol/L)        | 5.03 ± 1.42                | 4.57 ± 1.09              | t=4.084*     | <0.001* |
| IPTH (pg/mL)        | 726.26 ± 141.41            | 617.51 ± 139.98          | Z=5.240*     | <0.001* |

BUN: Blood urea nitrogen.

Po4: Phosphorus. IPTH: Intact parathyroid hormone.

t: Paired t-test Wilcoxon signed ranks test

There were significant lower levels of both Po4 and IPTH at the end of the study in low flux group with P value 0.018 and 0.040 respectively. No significant differences were found at the end of the study regarding hemoglobin and creatinine levels. In contrast to high flux group, pre and post-dialysis BUN levels increased at the end of the study, as shown in table 3.

**Table (3): Laboratory markers at the start and at the end of the study in Low flux group:**

|                     | At the start<br>Mean ± SD | At the end<br>Mean ± SD | Test of sig. | p       |
|---------------------|---------------------------|-------------------------|--------------|---------|
| Hemoglobin (g/dL)   | 9.58 ± 2.29               | 9.78 ± 1.51             | t=1.188      | 0.238   |
| Pre - dialysis BUN  | 67.42 ± 2.69              | 70.32 ± 2.77            | t=3.509*     | 0.001*  |
| Post - dialysis BUN | 34.87 ± 2.60              | 38.28 ± 3.63            | t=4.678*     | <0.001* |
| Creatinine (mg)     | 9.69 ± 2.53               | 9.73 ± 2.10             | t=0.316      | 0.753   |
| Po4 (mmol/L)        | 5.24 ± 1.51               | 4.93 ± 1.1              | t=2.412*     | 0.018*  |
| IPTH (pg/mL)        | 768.03 ± 89.27            | 697.87 ± 69.11          | Z=2.056*     | 0.040*  |

BUN: Blood urea nitrogen. Po4: Phosphorus.

IPTH: Intact parathyroid hormone.

Adequacy of dialysis in the form of Kt/V and URR showed also highly significant improvement at the end of the study in high flux group with P value <0.001, as shown in table 4.

**Table (4): Adequacy of dialysis at the start and at the end of the study in High flux patients:**

|             | At the start  | At the end    | Test of sig. | p       |
|-------------|---------------|---------------|--------------|---------|
| <b>Kt/V</b> |               |               |              |         |
| Min. – Max. | 0.600 – 2.150 | 0.608 – 2.410 | t=4.633*     | <0.001* |
| Mean ± SD.  | 1.130 ± 0.369 | 1.262 ± 0.439 |              |         |
| <b>URR</b>  |               |               |              |         |
| Min. – Max. | 34.68 – 84.58 | 39.77 – 89.50 | t=4.751*     | <0.001* |
| Mean ± SD.  | 59.43 ± 11.89 | 63.57 ± 12.42 |              |         |

URR: Urea reduction ratio.

There were no significant differences were found at the end of the study in low flux group regarding Kt/V and URR (Table 5).

**Table (5): Adequacy of dialysis at the start and at the end of the study in Low flux group:**

|             | At the start  | At the end    | Test of sig. | p     |
|-------------|---------------|---------------|--------------|-------|
| <b>Kt/V</b> |               |               |              |       |
| Min. – Max. | 0.604 – 1.688 | 0.610 – 1.899 | t=1.501      | 0.136 |
| Mean ± SD.  | 0.887 ± 0.243 | 0.927 ± 0.269 |              |       |
| <b>URR</b>  |               |               |              |       |
| Min. – Max. | 33.48 – 79.73 | 34.99 – 86.66 | t=1.732      | 0.086 |
| Mean ± SD.  | 50.46 ± 9.63  | 52.38 ± 10.46 |              |       |

URR: Urea reduction ratio.

## DISCUSSION

IDH (intradialytic SBP rise  $\geq 10$  mmHg at  $\geq 4$  over 6 consecutive sessions) is estimated at 5–15% of HD patients and is associated with poor prognosis<sup>(3)</sup>. It has been associated with poor clinical outcomes in HD patients and increased cardiovascular morbidity and mortality<sup>(4)</sup>.

Management of IDH patients should include an initial reassessment of dry weight. Patients with persistent IDH should be treated with less dialyzable drugs and there is some evidence that carvedilol may add a specific benefit. Modification of the dialysate sodium also to be considered, with careful monitoring of hemodynamics<sup>(2)</sup>.

The principle of HD involves the clearance of solutes across a semi-permeable membrane through diffusion and ultrafiltration mechanisms. Two types of membranes are used in HD procedure: **Low-flux dialyzers** with low permeability for water; and **high-flux ones**, non-celluloses membrane with higher permeability, which can remove moderate-sized molecules between 10000 to 15000 Dalton, including many inflammatory proteins and  $\beta_2$  microglobulin<sup>(15)</sup>.

The findings of these two randomized controlled trials (RCTs) [**Hemodialysis (HEMO) and Membrane Outcome Permeability (MPO)**] showed that the use of high-flux membranes is better than low-flux membranes in removal of larger molecules. However, questions remain regarding the significant effects of high-flux membranes on overall outcomes<sup>(16)</sup>.

Our objectives in the current study were to detect the incidence of IDH in HD patients and to compare the effect of high flux versus low flux dialysis on both; IDH and adequacy of dialysis in Beheira governorate.

Regarding demographic data, there were no significant differences between studied groups according to sex.

As regarding to IDH in HD patients in Beheira governorate, we found that the incidence is 23.5%. These results agreed with **Chen et al.**<sup>(7)</sup> who also reported that IDH occurs in 8% to 30% of treatments. In contrast, our results disagreed with **Bikos et al.**<sup>(3)</sup> who reported that IDH is estimated at 5–15% of HD patients, but the last study was conducted over smaller number of patients than our study.

Regarding the effect of high-flux vs low-flux dialysis on IDH at the start, after one month and at the end of the study, there were no statistically significant differences between both groups. Our results agreed with **Susantitaphong et al.**<sup>(17)</sup> who reported that the type of dialyzer did not have any impact on blood pressure. Also, our results agreed with **Ram & Fenves**<sup>(18)</sup> who suggested that multiple mechanisms may be involved in the control of blood pressure other than HD alone. We found that there was a significant decrease in number of IDH patients after one month duration and after three months in both high-flux and low-flux

dialysis patients. This coincides with the previous study mentioned above.

In contrast to our data, **Fadel et al.**<sup>(19)</sup> showed that the pre-dialytic mean arterial pressure (MAP) was significantly lower in the high flux group than in the low flux group. This finding also agrees with the results found by **Li et al.**<sup>(20)</sup> who recorded also a significant reduction in blood pressure in their patients after the switch to high-flux dialyzers.

Clinical experience and experimental data suggest that intradialytic hemodynamic profiles could be influenced by the characteristics of the dialysis membranes. The low-flux membrane correlated to higher blood pressure levels compared with the high-flux ones<sup>(21)</sup>.

Our results showed no significant difference between studied groups as regards etiology of ESRD, HD duration, vascular access and anti-hypertensive drugs used.

In our study, there was significant improvement in the form of reductions in all of pre-dialysis BUN, post-dialysis BUN and serum creatinine levels at the end of the study in high flux group matching **El Arbagy et al.**<sup>(22)</sup> and **Krieter & Canaud**<sup>(23)</sup> results. High flux filters with large pore sizes are efficient in removal of toxins with medium weight, but on the other hand, other smaller substances may be markedly decreased.

Also, adequacy of dialysis in the form of Kt/V and URR showed highly significant improvement by the end of the study in the high flux group. Our results matched **Oshvandi et al.**<sup>(15)</sup> and **Isemi et al.**<sup>(24)</sup> results and disagreed with **Palmer et al.**<sup>(25)</sup>. The high-flux membrane had better dialysis adequacy, so we suggest using high-flux membrane in HD centers; as our results showed significant difference between studied groups as regards adequacy of dialysis.

By the end of our study serum hemoglobin levels were significantly improved in high flux group compared to the low flux one. This agreed with **Ayli et al.**<sup>(26)</sup> who suggested that high-flux membranes eliminate molecules of medium molecular weight that accumulate in renal failure and have harmful effects on erythropoiesis and disagrees with **Schneider et al.**<sup>(27)</sup> in MINOXIS Study who found that high-flux dialysis had no superior effects on haemoglobin levels.

Decrease in bone mineral density (BMD) is a common finding in patients with CKD, especially those on dialysis. Bone profile blood tests (Ca – Po4 – IPTH) are simple measures of mineral-bone disease. High-flux membranes are more efficient than low-flux ones in removal of parathyroid hormone molecule, and they may help in reducing the consequences of bone disease associated with hyperparathyroidism in patients with ESRD<sup>(28)</sup>. This matches our results as there was more significant improvement and reduction in serum IPTH levels in the high flux group compared to the low flux group by the end of the study.

In the studies of *Ayli et al.* <sup>(26)</sup>, *Makar et al.* <sup>(28)</sup> and *El Arbagy et al.* <sup>(29)</sup>, there were no significant differences between use of low flux dialysis and high flux dialysis as regards calcium levels but there was significant decrease in serum phosphorus after use of high flux dialysis compared to low flux dialysis. Past three studies coincide with our results, as there was highly significant decrease in serum Po<sub>4</sub> levels at the end of the study in the high flux group. *Gallar et al.* <sup>(30)</sup> suggested that membrane permeability does not influence the phosphate removal.

*Locatelli et al.* <sup>(31)</sup> mentioned that serum levels of sodium, potassium and calcium and changes in levels of these electrolytes during HD are important because of the close relationship between levels of these electrolytes and myocardial contractility, peripheral vascular resistance, and BP control and so their role in pathology and management of IDH. Our results showed no significant differences between effect of high-flux vs low-flux dialysis on Na, K and Ca levels. This disagrees with *El Arbagy et al.* <sup>(22)</sup> who showed a significant decline of serum sodium, potassium levels after the use of high flux filters.

Not all studies reported beneficial effects of high-flux HD on lipid abnormalities but revealed at least a reduction in triglyceride levels <sup>(32)</sup>. The last study matches our results as there were significant differences between effects of high-flux vs low-flux dialysis on triglycerides levels.

## CONCLUSION

It could be concluded that the current study has not demonstrated a significant difference in the effect of high flux versus low flux dialysis on IDH, but there was significant improvement in adequacy of dialysis in the form of Kt/V and URR by the end of the study in the high flux group compared to the low flux group. Also, there was significant improvement in all of pre-dialysis BUN, post-dialysis BUN, serum creatinine levels and serum IPTH levels by the end of the study in the high flux group compared to the low flux group.

**Limitations of the study:** Compared to some other studies, follow-up of the patients was only 3 months which may be relatively short to demonstrate the effect of both modalities of dialysis on IDH.

**Conflict of interest:** The authors declare no conflict of interest.

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**Author contribution:** Authors contributed equally in the study.

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