Randomized Controlled Trial of Medium Cut-Off versus High-Flux Dialyzers on Quality of Life Outcomes in Maintenance Hemodialysis Patients

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BACKGROUND

Patients on maintenance hemodialysis suffer from symptoms such as fatigue, generalized weakness, and pruritus. These subjective conditions are assumed to be related to the accumulation of middle molecules that are not cleared by conventional hemodialysis (HD). Middle molecules have molecular weights (MWs) ranging between 500 and 60,000 Daltons, and their size is a barrier to removal with dialyzers. The accumulation of middle molecules is associated with specific complications such as amyloidosis, inflammatory reactions, oxidative stress, and endothelial dysfunction. Consequently, middle molecules contribute to morbidity and mortality and poor quality of life (QOL) in in patients with end-stage renal disease (ESRD).

Compared with high-flux dialyzers and hemodiafiltration (HDF), medium cut-off dialyzers may improve the removal of middle molecules due to their higher permeability and increased convective transport, but clinical data on the effects of **MCO** dialyzers on patient-reported outcomes are lacking.

OBJECTIVE

This study aimed to investigate potential QOL improvement using **MCO** dialyzers in patients undergoing maintenance HD with a high-flux dialyzer. This study also sought to evaluate the effect of **MCO** dialyzers on the removal of middle molecules and pre-dialysis plasma concentrations.

METHODOLOGY

Study Design

This study was a randomized, prospective, controlled, open-label, phase 4 trial in patients treated with maintenance HD at a national university hospital in South Korea. Patients aged 18 years or older, had been receiving maintenance high-flux membrane HD for more than three months, had vascular access by arteriovenous fistula/graft and adequate dialysis were enrolled.

Patients were randomly assigned into **MCO** dialyzer and high-flux groups at 1:1 ratio. Patients and physicians were unblinded to the assignment. The **MCO** dialyzer group switched from a high-flux membrane (Fx CorDiax 60 or 80; Fresenius Medical Care Deutschland, Bad Homburg, Germany) to a **Theranova** 400 dialyzer (Baxter International Inc., Hechingen, Germany) and the high-flux group continued with a high-flux membrane.

Data Collection and Analysis

Patients completed the Kidney Disease Quality of Life-Short Form (KDQOL-SF) questionnaire. Uremic pruritus was assessed using the modified scoring questionnaire consisting of severity, distribution, and sleep disturbance categories. Questionnaires about QOL and pruritus were completed at baseline and at 12 weeks. Blood samples to identify middle molecule removal were obtained before and at the end of dialysis.

Study Outcomes

The primary outcomes were the KDQOL-SF and pruritus assessment. For the KDQOL-SF, analysis identified differences between the **MCO** dialyzer and high-flux groups, pre- and post-dialysis, in the questionnaire's 26 categories. For pruritus assessment, analysis identified differences in questionnaire responses between the two groups, pre- and post-dialysis, on severity and distribution by time of day (morning, afternoon), sleep disturbance, and scoring of responses to a visual analog scale.

The secondary outcomes were pre-dialysis plasma concentrations and reduction ratios (RRs) of middle molecules at baseline and 12 weeks after randomization. Analysis identified differences between the **MCO** dialyzer and high flux groups, pre-and post-dialysis, in levels of three middle molecules: β2-microglobulin (molecular weight (MW) 11.8 kDa[1]), a small middle molecule, and kappa free light chain [κ FLC] (22.5 kDa[1]) and lambda free light chain [λ FLC](45 kDa[1]), larger middle molecules.

Study Limitations

This study has several limitations. The sample size was small, and the study duration was insufficient to evaluate definite effects of the **MCO** membrane. The **Theranova** 500 dialyzer, which has a greater surface area (2.0 m^2) than the **Theranova** 400 dialyzer (1.7 m^2), was not applied in the **MCO** dialyzer group because the **Theranova** 500 dialyzer has not yet been introduced in South Korea. The actual extent of solute removal could not be estimated, or the exact pathophysiologic correlations proven between middle molecules and the physical components of QOL and uremic pruritus.

RESULTS

Patient Characteristics

A total of 50 patients were enrolled and one patient withdrew consent, resulting in 49 patients who completed the study. Twenty-four patients were in the **MCO** dialyzer group and 25 were in the high-flux group. No significant between-group differences in age, sex, body mass index, dry weight, daily urine volume, vascular access, baseline dialyzer, and dialysis vintage were observed.

Comparison of QOL Scores

The baseline perceptions of QOL assessed by the KDQOL-SF were similar in both groups. After 12 weeks, the physical function domain score was better in the **MCO** dialyzer group than in the high-flux group and the role-physical function domain score was also higher in the **MCO** dialyzer group. See Table 1. The effect of the **MCO** dialyzer on QOL is likely related to the better removal of middle molecules compared to high flux dialyzers. The improvements in the physical components of the QOL questionnaire over a relatively short exposure period occurred concurrently with the change of the dialyzer.

Reduction ratio (%)	Baseline			12 weeks		
	MCO dialyzer (*n* = 24)	High-flux (*n* = 25)	*P*	MCO dialyzer (*n* = 24)	High-flux (*n* = 25)	*P*
Total score	63.7 ± 13.8	57.0 ± 16.4	0.134	63.9 ± 14.4	59.0 ± 17.3	0.283
Kidney disease targeted items	67.9 ± 11.4	62.9 ± 12.3	0.142	66.2 ± 13.3	66.2 ± 12.9	0.995
Symptoms	81.9 ± 13.8	75.4 ± 14.0	0.107	81.3 ± 14.9	78.3 ± 14.6	0.471
Effects of kidney disease	67.6 ± 14.9	60.7 ± 18.9	0.163	65.1 ± 20.3	67.6 ± 18.9	0.654
Burden of kidney disease	40.9 ± 24.4	31.5 ± 26.1	0.200	39.3 ± 27.2	30.8 ± 23.5	0.244
Work status	14.6 ± 27.5	14.0 ± 30.7	0.945	12.5 ± 26.6	18.0 ± 35.0	0.540
Cognitive function	82.5 ± 19.0	83.7 ± 13.6	0.795	78.1 ± 24.1	84.0 ± 17.6	0.328
Quality of social interaction	67.8 ± 18.3	60.5 ± 15.0	0.136	68.1 ± 22.7	67.5 ± 20.3	0.927
Sexual function	57.5 ± 28.8	40.6 ± 42.5	0.500	45.8 ± 35.9	50.0 ± 70.7	0.911
Sleep	64.1 ± 19.3	60.9 ± 17.7	0.553	62.6 ± 15.1	61.6 ± 18.6	0.837
Social support	66.0 ± 22.2	66.0 ± 23.3	0.997	61.8 ± 23.3	73.3 ± 22.1	0.082
Dialysis staff encouragment	87.0 ± 14.0	85.5 ± 16.4	0.736	85.9 ± 15.3	85.5 ± 17.9	0.927
Patient satisfaction	61.8 ± 23.8	60.7 ± 23.0	0.866	61.1 ± 20.1	59.3 ± 22.6	0.773
Short form 36 items	58.9 ± 18.7	50.4 ± 22.6	0.158	61.5 ± 17.7	51.0 ± 24.1	0.088
PCS	61.4 ± 21.7	51.4 ± 25.8	0.150	62.8 ± 20.5	51.7 ± 25.8	0.100
Physical functioning	72.1 ± 23.7	59.4 ± 28.3	0.096	75.2 ± 20.8	59.8 ± 30.1	0.042
Role-physical	56.3 ± 39.2	44.0 ± 40.4	0.287	61.5 ± 37.6	39.0 ± 39.6	0.047
Pain	70.9 ± 22.9	65.0 ± 28.2	0.424	72.2 ± 24.9	69.3 ± 24.1	0.682
General health	37.9 ± 18.7	36.0 ± 26.0	0.768	35.4 ± 20.1	38.4 ± 27.3	0.666
MCS	55.8 ± 18.1	49.2 ± 21.1	0.249	60.2 ± 16.4	50.5 ± 23.8	0.104
Emotional well-being	54.7 ± 16.0	57.9 ± 18.6	0.515	61.7 ± 16.1	53.4 ± 21.8	0.141
Role-emotional	61.1 ± 40.1	38.7 ± 44.8	0.071	62.5 ± 38.5	45.3 ± 45.0	0.159
Social function	70.3 ± 21.1	62.0 ± 28.1	0.249	69.8 ± 23.6	64.0 ± 26.6	0.425
Energy/fatigue	45.8 ± 20.7	39.8 ± 18.6	0.289	51.7 ± 17.9	43.8 ± 21.6	0.173
Health status compared to one year ago	51.0 ± 21.5	46.0 ± 25.7	0.461	53.1 ± 23.7	46.0 ± 24.7	0.308
Overall health rate	57.9 ± 22.1	56.4 ± 25.2	0.824	58.8 ± 22.5	50.0 ± 26.3	0.218

TABLE 1. Quality of life questionnaire scores at baseline and 12 weeks. Values are shown as the + standard deviation. Abbreviations: PCS, physical composite summary; MCS, mental composite summary. Adapted from Lim et al.

Comparison of Pruritus Scores

The morning pruritus intensity was worse in the **MCO** dialyzer group than in the high-flux group at baseline, but this difference was not observed at 12 weeks. After 12 weeks, the pruritus distribution in the morning was smaller in the **MCO** dialyzer group than in the high-flux group. The **MCO** dialyzer group also had less frequent sleep disturbances caused by pruritus-related scratching. See Table 2.

Comparison of Middle Molecule Concentrations and Reduction Ratios

The serum pre-dialysis and post-dialysis levels of the of three middle molecules (β2-microglobulin, κFLC, and λFLC) did not differ between the **MCO** dialyzer and high-flux groups at baseline or at 12 weeks. However, the **MCO** dialyzer displayed better removal of κFLC and λFLC compared with the high-flux dialyzer. The removal of λFLC was significant, $p < 0.001$. See Table 2.

Comparison of Laboratory Data, Ultrafiltration Volume, and Dialysis Adequacy

No significant differences in biochemical markers including serum albumin (65 kDa[1]), ultrafiltration volume, and dialysis adequacy between the **MCO** dialyzer and high-flux groups at baseline and at 12 weeks were found.

Reduction ratio (%)	Baseline			12 weeks		
	MCO (*n* = 24)	High-flux (*n* = 25)	*P*	MCO (*n* = 24)	High-flux (*n* = 25)	*P*
Severity						
Morning	1.92 ± 1.06	1.40 ± 0.50	0.033	1.54 ± 0.72	1.64 ±0.86	0.667
Afternoon	2.00 ± 1.14	1.72 ± 0.84	0.332	1.88 ± 0.95	1.84 ± 1.07	0.904
Distribution						
Morning	1.42 ± 0.58	1.48 ± 0.71	0.736	1.29 ± 0.46	1.64 ± 0.64	0.034
Afternoon	1.46 ± 0.59	1.56 ± 0.96	0.659	1.38 ± 0.65	1.56 ± 0.71	0.347
Sleep disturbance						
Frequency of waking from sleep	0.83 ± 1.05	0.68 ± 1.28	0.650	0.75 ± 0.85	1.32 ± 1.60	0.126
Frequency of scratching during sleep	0.38 ± 0.92	0.24 ± 0.72	0.571	0.25 ± 0.53	1.00 ± 1.47	0.023
Total score by measuring system	8.58 ± 7.74	7.20 ± 7.58	0.530	6.92 ± 5.98	9.92 ± 8.23	0.152
VAS scoring system						
Morning	2.58 ± 2.24	2.14 ± 2.28	0.496	2.50 ± 1.93	3.34 ± 2.82	0.232
Afternoon	3.04 ± 2.57	2.74 ± 2.53	0.680	3.46 ± 2.32	4.24 ± 3.18	0.333
Average	2.81 ± 2.19	2.44 ± 2.31	0.565	2.98 ± 1.98	3.79 ± 2.91	0.262

TABLE 2. Assessment of uremic pruritus at baseline and 12 weeks. Abbreviations: **MCO** dialyzer, medium cut-off; VAS, visual analog scale. Adapted from Lim et al.

Adverse Events

No serious adverse events including cardiovascular events, death, or blood pressure decline that required dialyzer changes were observed.

CONCLUSION

This is the first randomized controlled prospective trial comparing the effects of the **MCO** dialyzer and high-flux dialyzers on QOL in patients receiving maintenance HD. The higher physical functioning and role-physical scores with **MCO** dialyzer than with high-flux membrane found in this study were consistent with prior studies and is likely related to the better removal rate of middle molecules in the **MCO** dialyzer group than in the high-flux group. The **MCO** dialyzer group also had less frequent sleep disturbances caused by pruritus-related scratching. The new **MCO** dialyzer may improve self-reported QOL, particularly in the physical domains and uremic pruritus, in patients receiving maintenance HD who use permanent dialysis access. The **MCO** dialyzer also had a non-significant effect on the serum albumin concentration over 12 weeks of treatment.

MCO membrane may improve patient-reported outcomes, particularly in the physical domains of QOL and uremic pruritus, through efficient removal of middle molecules, in stable maintenance HD patients.

1. Wolley M, Jardine M, Hutchison CA. Exploring the clinical relevance of providing increased removal of large middle molecules. *Clin J Am Soc Nephrol*. 2018; 13:805-814.

The **Theranova** dialyzer is indicated for patients with chronic kidney failure who are prescribed intermittent hemodialysis. It provides an expanded solute removal profile with increased removal of various middle molecules (up to 45 kDa) that may play a pathologic role in the uremic clinical syndrome. The **Theranova** dialyzer is not intended for hemofiltration or hemodiafiltration therapy. The total extracorporeal blood volume for the **Theranova** dialyzer and the set should represent less than 10% of the patient's blood volume. For single use only.

Rx only. For safe and proper use of these devices refer to the Instructions for Use.