Medium Cut-Off Dialyzer Improves Erythropoiesis Stimulating Agent Resistance in a Hepcidin-Independent Manner in Maintenance Hemodialysis Patients: Results from a Randomized Controlled Trial

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BACKGROUND

Anemia is a frequent complication of end-stage kidney disease (ESKD) and is associated with increased morbidity and mortality rates. Anemia in ESKD has multiple causes, including erythropoietin deficiency, uremia-related inhibition of erythropoiesis, and inflammation. Erythropoiesis stimulating agents (ESAs) and iron are used to treat anemia in ESKD patients. However, the responses to ESA vary greatly due to iron deficiency, poor nutritional state, and chronic inflammation. Patients who have been on maintenance hemodialysis regularly exhibit this resistance, which also has a cumulative effect over time.

Uremic toxins are associated with chronic inflammation and are known to affect iron metabolism in ESKD patients by interfering with the response to ESAs. There are uremic substances of various sizes that cause ESA resistance, including hepcidin and inflammatory cytokines. Traditional hemodialysis (HD) effectively removes small molecular uremic toxins but has limited capacity to remove large middle molecules, which is believed to improve ESA response.

Newly introduced medium cut-off dialyzers have uniformly distributed larger pores and have a greater capacity to remove conventional/large middle molecules and inflammatory cytokines compared to traditional high-flux (HF) dialyzers. However, there is no clear evidence that demonstrates the effect of **MCO** dialyzer membranes on ESA resistance in maintenance HD patients.

OBJECTIVE

This study aimed to evaluate whether the **MCO** dialyzer membrane can improve the ESA resistance in chronic HD patient.

METHODS

Study Design

This is a post-hoc analysis of a prospective, randomized, controlled, open-label trial in patients treated with maintenance HD, at a national university hospital in South Korea, for a study period of 12 weeks. The original trial evaluated the impact of the **MCO** dialyzer membrane on quality of life compared to HD with high flux dialyzer.* The post-hoc analysis evaluated the impact of the **MCO** dialyzer membrane on ESA resistance.

*Lim et al. Randomized Controlled Trial of Medium Cut-Off versus High-Flux Dialyzers on Quality of Life Outcomes in Maintenance Hemodialysis Patients. Nature/Sci Rep. 2020; 10:7780. A summary of this study can be found in this compendium.

In the original trial, patients were randomly allocated in a 1:1 ratio to the **MCO** dialyzer membrane (**MCO** dialyzer group) and high-flux dialyzer (HF HD group). The HDx-MCO group changed their dialysis membrane from a high-flux dialyzer (FX CorDiax 80 or 60; Fresenius Medical Care Deutschland, Bad Homburg, Germany) to a **MCO** dialyzer (**Theranova** 400; Baxter International Inc., Hechingen, Germany). The HF HD group continued their treatments with the high-flux dialyzer. There was no change in the dialysis prescription for dialysis time per session, dialysis frequency per week, blood flow rate, and dialysate flow rate during the study period.

Data Collection and Analysis

Data collected in the original trial was used for this post-hoc analysis. Baseline demographics, comorbid diseases, biochemical data, and dialysis information were collected at the time of enrollment. The erythropoietin resistance index (ERI), calculated as the mean weekly weight-adjusted ESA dose divided by the hemoglobin level, was used to evaluate the ESA resistance; the level was measured every 4 weeks. Blood samples for the measurement of biochemical markers were obtained at the start of a midweek dialysis session. All the baseline samples were collected while patients were being dialyzed with high-flux HD.

Study Outcomes

The primary outcome was ESA resistance change, defined as the change in ERI after 12 weeks of treatment with either HF HD or **MCO** dialyzer therapy. The secondary outcomes were iron- and anemia-related markers, reduction ratios of the iron regulator (hepcidin), and the inflammatory cytokine tumor necrosis factor-alpha (TNF-α), after 12 weeks of treatment with either HF HD or **MCO** dialyzer therapy.

Study Limitations

The number of registered patients was small (n=49), and the study duration (12 weeks) was not long enough to get definite results. Although anemia-related parameters such as iron, transferrin saturation (TSAT), and TNF-α, were significantly different at 12 weeks, the within-group differences were not significant for these parameters. The study was not blinded to clinicians and could have affected the prescription of ESA and iron supplementation. Finally, the detailed mechanism regarding how ESA response was improved by increased removal of conventional/large middle molecules remains unclear.

RESULTS

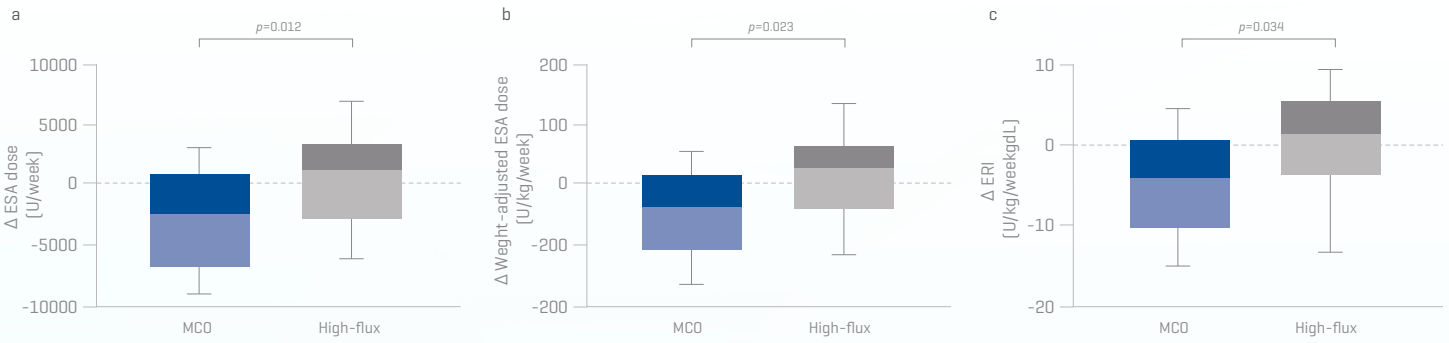
Patient Characteristics

All the enrolled patients (n=49) completed the study except one patient who withdrew consent in the **MCO** dialyzer group. The age, sex, residual renal function, type of dialyzer, dialysis method, comorbidities and ESA treatment were well balanced between the two groups.

Primary Outcome: Change in ERI (Reflecting ESA Resistance)

MCO dialyzer membrane reduced ESA resistance compared to high flux HD. A comparison of differences (Δ) in the baseline and 12 weeks' values of ESA dose and weight-adjusted ESA dose showed significantly lower values in the **MCO** dialyzer group, than in the high flux group (Δ ESA dose, p=0.012; Δ weight-adjusted ESA dose, p=0.023). The difference in ERI was significantly lower in the **MCO** dialyzer group than in the high-flux group (Δ ERI, p=0.034). See Figure 1.

Figure 1. Comparison of ESA (a), weight-adjusted ESA (b), and ERI (c) difference. Abbreviations: ESA, erythropoiesis stimulating agent; ERI, erythropoietin index. Figure adapted from Lim et al.



Secondary Outcome: Iron Metabolism and Anemia-Related Markers

- The serum iron level and TSAT after 12 weeks of therapy were significantly higher in the **MCO** dialyzer group than the HF HD group, despite the comparable use of intravenous (IV) iron (iron, p=0.029; TSAT, p=0.031)
- Other parameters of iron metabolism such as erythroferrone (ERFE), erythropoietin (EPO), and soluble transferrin receptor (sTfR) were not significantly different between the HF HD and the **MCO** dialyzer groups, at baseline or after 12 weeks of therapy
- Serum hepcidin level was not different between groups at baseline or after 12 weeks of therapy
- TNF-α level was significantly lower in the **MCO** dialyzer group compared to the HF HD group, after 12 weeks of therapy
- Biochemical data for serum hemoglobin, albumin, and high-sensitivity C-reactive protein (hsCRP) levels were similar between groups at the start and end of the study, and the changes during the study were not significant. See Table 1.
- The changes in these iron metabolism and biochemical parameters did not show significant differences between groups

Secondary Outcome: Comparison of the Reduction Ratio (RR) of Serum Hepcidin and TNF-α

The RR of serum hepcidin was not significantly different between the HF HD and **MCO** dialyzer groups at baseline or after 12 weeks of therapy. The RR of TNF-α was similar at baseline for the HF HD and **MCO** dialyzer groups; however, after 12 weeks, it was higher in the **MCO** dialyzer group than in the HF HD group (p = 0.025). See Figure 2.

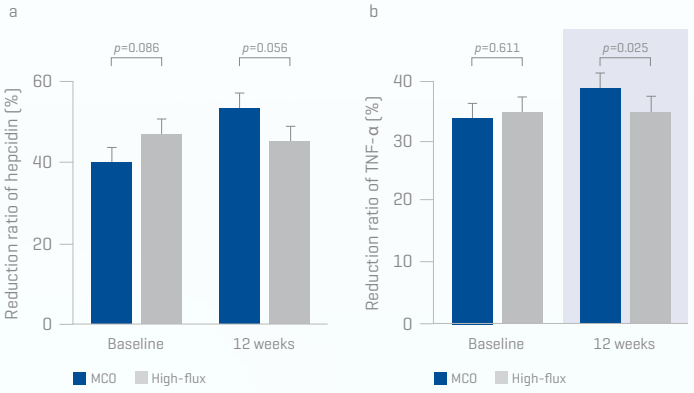


Figure 2. Reduction ratio of serum hepcidin (a) and TNF-α (b) at baseline and 12 weeks. Abbreviation: TNF-α, tumor necrosis factor-alpha. Figures adapted from Lim et al.

DISCUSSION AND CONCLUSIONS

Changing from HD with high-flux dialyzer to HD with the **MCO** dialyzer membrane improved the ESA resistance as compared to continuing HD with high-flux dialyzer. The importance of ESA resistance in HD patients has been emphasized in several reports; ESA hyporesponsive HD patients have shown increased all-cause mortality and cardiovascular complications. Although the impact of improved ESA resistance on mortality and cardiovascular events was not evaluated in this study, it might have a positive effect on the prognosis in the long-term.

	Baseline			12 weeks			Difference (Δ) between baseline and 12 weeks		p for difference (Δ) between groups
	MCO	High-flux	p	MCO	High-flux	p	MCO	High-flux	
Hemoglobin (g/dL)	10.6 ± 0.9	10.7 ± 1.1	0.859	10.9 ± 0.9	11.0 ± 1.0	0.697	0.2 (-0.5, 0.0)	0.0 (-0.3, 0.9)	0.841
Albumin (g/dL)	4.11 ± 0.38	4.06 ± 0.33	0.635	3.98 ± 0.27	4.04 ± 0.33	0.450	-0.05 (-0.30, 0.00)	-0.10 (-0.20, 0.15)	0.252
hs-CRP (mg/dL)	0.11 (0.03,0.26)	0.18 (0.05, 0.71)	0.704	0.13 (0.04, 0.46)	0.22 (0.06, 1.30)	0.250	0.00 (-0.10, 0.17)	0.06 (-0.03, 0.78)	0.161
Ferritin (ng/mL)	161.1 (70.1, 305.3)	90.3 (38.6, 205.9)	0.156	123.9 (57.9, 312.2)	158.1 (59.5, 284.2)	0.904	19.2 ± 173.6	19.1 ± 151.7	0.998
Iron (μg/dL)	66.1 ± 25.0	59.6 ± 29.8	0.410	72.1 ± 25.4	55.9 ± 25.0	**0.029**	2.49 (-5.9, 15.8)	-1.6 (-15.8, 4.0)	0.131
TIBC (μg/dL)	221.4 ± 37.8	234.8 ± 51.7	0.309	221. 1 ± 46.3	227.1 ± 33.9	0.607	-0.3 ± 36.3	-7.7 ± 32.2	0.455
TSAT (%)	30.6 ± 12.3	26.1 ± 11.9	0.196	34.0 ± 15.0	25.3 ± 11.9	**0.031**	-0.6 (-4.4, 8.1)	0.8 (-8.5, 3.7)	0.325
ERFE (pg/ml)	402.5 ± 122.3	360.3 ± 136.0	0.259	483.3 ± 123.0	386.0 ± 116.2	0.133	53.0 (-38.3, 95.8)	44.6 (0.8, 73.6)	0.660
EPO (mU/mL)	9.5 (6.7,16.0)	11.9 (5.0,18.5)	0.818	10.1 (4.6, 19.9)	7.9 (5.3, 15.3)	0.741	-2.3 (-6.5, 6.2)	0.5 (-9.5, 3.2)	0.889
sTfR (nmol/L)	16.7 (12.8, 23.5)	17.8 (13.6, 23.7)	0.617	16.4 (11.3, 21.9)	18.5 (11.1, 23.6)	0.660	-1.4 ± 8.3	-1.5 ± 10.1	0.981
Hepcidin (ng/mL)	46.8 ± 36.9	32.4 ± 27.3	0.128	42.1 ± 23.8	44.9 ± 26.3	0.688	-3.5 ± 31.1	12.3 ± 27.0	0.063
TNF-α (pg/mL)	17.9 ± 5.0	18.0 ± 4.7	0.915	16.3 ± 3.4	19.0 ± 4.8	**0.027**	-1.6 ± 4.3	1.0 ± 5.7	0.079

Table 1. Comparisons of the iron metabolism and biochemical parameters. Data are shown as mean ± standard deviation or median (interquartile range). Values in bold indicate statistically significant results. Abbreviations: TSAT, transferrin saturation; ERFE, erythroferrone; EPO, erythropoietin; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TNF-α, tumor necrosis factor-alpha, hs-CRP, high sensitivity C-reactive protein. Table adapted from Lim et al.

The improvement in ESA resistance using the **MCO** dialyzer membrane may be attributable to the efficient removal of conventional/large middle molecules including TNF-α. Under uremic conditions, chronic inflammation may induce an enhanced state of T-cell activation that leads to ESA resistance. TNF-α (molecular weight (MW) 17.3 kDa) is a representative pro-inflammatory cytokine that is usually elevated with chronic kidney disease. TNF-α causes anemia by inhibiting erythroid-precursor proliferation and promoting hypoferremia. The study confirmed that switching to the **MCO** dialyzer membrane resulted in improved TNF-α removal, as shown by lower TNF-α level after 12 weeks in the **MCO** dialyzer group, as compared to patients who continued with HF HD. Changes in erythropoiesis and iron metabolism-related parameters, such as hepcidin, erythroferrone, erythropoietin were analyzed to investigate the association between TNF-α and ESA resistance. TNF-α induces hypoferremia through both hepcidin-independent and hepcidin-dependent mechanisms. Hepcidin is a relatively small-sized (~27 kDa) large middle molecular uremic toxin that has an effect on ESA resistance. The serum hepcidin level is typically controlled by inflammation and erythropoietin. While the RR and difference in hepcidin at baseline and after 12 weeks of therapy did not vary significantly between groups, after 12 weeks of the **MCO** dialyzer group hepcidin levels decreased by 3.5 ng/mL vs. an increase of 12.3 ng/mL in the HF HD group (p=0.063). There was no significant difference between groups in serum level of erythropoietin (30.4 kDa), a regulator of hepcidin, with a decrease of 2.3 mU/mL in the **MCO** dialyzer group, vs. an increase of 0.5 mU/mL in the HF HD group. Erythroferrone (52 kDa), also a regulator of hepcidin, remained unchanged after switching to the **MCO** dialyzer, which further supports the **Theranova** dialyzer's ability to retain larger (>45 kDa) proteins and essential substances. Considering these results, it is possible that the hepcidin-independent pathway played a dominant role in improving iron status, in this study.

In conclusion, the **MCO** dialyzer membrane achieved greater improvement in ESA resistance than HD with high-flux dialyzer. The **MCO** dialyzer membrane efficiently removed the conventional/large middle molecule TNF-α, an inflammatory cytokine, potentially influencing iron metabolism.

MCO dialyzer membrane improves ESA resistance over time compared to high-flux HD in maintenance HD patients. MCO dialyzer membrane provides superior removal of large middle molecules, reducing inflammatory cytokines potentially improving iron metabolism.

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Theranova dialyzers are indicated for treatment of chronic and acute renal failure by Hemodialysis. For single use only.

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

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