A tRial Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in Hemodialysis Patients (REMOVAL-HD): A Safety Device Study

Krishnasamy R, Hawley CM, Jardein MJ,. A trial evaluating mid out-off value membrane clearance of albumin and light chains in hemodialysis patients (REMOVAL-HD): a safety device study. *Blood Purif.* 2020; 1-11. doi: 10.1159/000505567.

BACKGROUND

Patients with end-stage kidney disease (ESKD) are often burdened with a myriad of complications including cardiovascular disease, infection, and malnutrition resulting in high rates of hospitalization, reduced quality of life and increased risk of death. Retention of uremic toxins, especially middle molecules that are not well cleared by current dialysis therapies, may contribute to the disease burden in the ESKD cohort.

The clearance of middle molecules has continued to improve with the evolution of dialysis technology over the last 20 years. With the advent of high-flux dialyzers and hemodiafiltration (HDF), the efficiency of middle molecule clearance by chronic hemodialysis (HD) has continually increased; however, the clearance of almost a third of the larger middle molecules (>25kDa) is yet to be optimized. Pore sizes of dialysis membranes are crucial in determining the clearance of larger middle molecules. However, membranes with larger pore sizes such as the high cut-off dialyzer were associated with substantial albumin loss (molecular weight (MW) (65kDa[1]), requiring albumin supplementation following dialysis treatment. This resulted in the view that high cut-off membranes were unsafe and impractical for maintenance HD.

Advancements have led to the development of a new class of dialysis membranes called the mid cut-off dialyzer. This membrane has a pore size between that of a standard high flux and an high cut-off membrane with narrowly distributed pores to enhance membrane permeability and selectivity. However, the safety and efficiency data for the **MCO** dialyzer in a clinical setting are limited.

OBJECTIVE

The primary aim of a tRial Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in Hemodialysis Patients (REMOVAL-HD) study the was to determine the safety of HD using a **MCO** dialyzer (**Theranova** dialyzer; Vantive Health, Sydney, Australia) with regard to its effect on change in serum albumin over 6 months in a prevalent HD cohort.

METHODOLOGY

The study was an investigator initiated, open label, non-randomized, cross over, longitudinal device study conducted across 9 centers in Australia and New Zealand (n=89). Recruitment commenced in January 2017 and the last participant follow-up occurred in April 2018. The criteria for inclusion included >18 years of age, had been on chronic in-center HD for at least 12 weeks.

All visits occurred during participants' mid-week HD session. See Figure 1. Study schema was as follows:

> **Wash-in period (week 0-4)**
Participants used a 4-week HD wash-in period using a high flux dialyzer (**Revaclear** R400; Vantive Health, Sydney, Australia).

> **Intervention period (week 4-28)**
Participants then received 24 weeks of treatment with the investigational device, the **MCO** dialyzer (**Theranova** 400 dialyzer; Vantive Health, Sydney, Australia).

> **Wash-out period (week 28-32)**
Participants then received a 4-week wash-out period using the **Revaclear** high flux dialyzer again.

Centers were advised to maintain the duration (3.0-5.5 hours/session) and frequency of dialysis (3x/week), target blood flow (> 300 mL/minute) and dialysate flow rate (DFR) (500 mL/minute) throughout the study period.

Outcome Measures

Primary Outcomes

The primary outcome was change in centrally measured pre-dialysis serum albumin between baseline (week 4) and 6 months (week 28) during the treatment phase of HD with the **MCO** dialyzer. Other safety outcomes included change in serum albumin across all study visits during the treatment phase monitoring of any large (> 25%) reductions in serum albumin level at every visit. In addition, serious adverse events (SAE) were recorded regardless of whether they were related to the study intervention using standard criteria for clinical trials.

Study Procedures

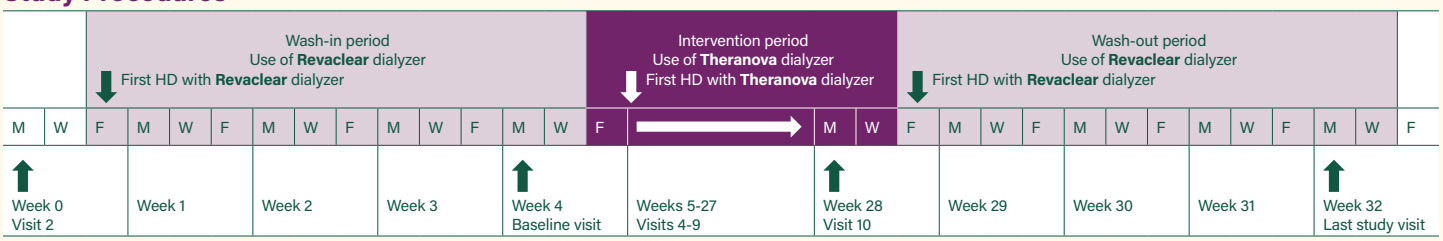

FIGURE 1. REMOVAL-HD study schema. Adapted from Krishnasamy et al. Abbreviations: HD, hemodialysis.

Secondary Outcomes
Secondary outcomes included change in pre-dialysis serum level of middle molecules (lambda-free light chains [FLC] (45 kDa), kappa-FLC (22.5 kDa) and β2-microglobulin (11.8 kDa)).

RESULTS

Eighty-nine (89) participants started the **MCO** dialyzer HD intervention and provided analyzable data and 87 were sufficiently compliant with the intervention (at least 80% use of **MCO** dialyzer) to be included in the main analysis of the primary outcome.

Serum Albumin

Serum albumin 65 kDa[1] levels were stable over 6 months and the overall albumin concentration decline was minimal at 0.7 g/L. See Table 1. In addition, an immediate decline in serum albumin following commencement of the **MCO** dialyzer was not seen. See Figure 2. A sustained, unexplained reduction in serum albumin of >25% for 2 consecutive visits was not observed in any participant.

Timing	Measurement of Serum Albumin (n=87)	*p* value
Baseline (Week 4)	35.8 ± 3.9 g/L	
6 Months (Week 28)	35.1 ± 4.0 g/L	
Reduction (6 Months-Baseline)	−0.7 g/L (95% CI −1.5 to 0.1)	0.1

TABLE 1. Measurement of serum albumin and reduction. Adapted from Krishnasamy, et al. Abbreviations: CI, confidence interval.

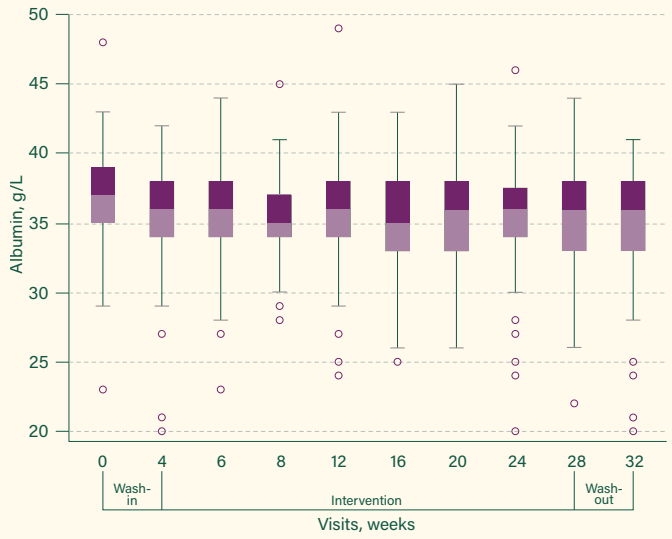

FIGURE 2. Measurement of serum albumin and reduction. Adapted from Krishnasamy, et al. Abbreviations: CI, confidence interval.

Middle Molecules

A reduction in FLC was observed 2 weeks into **MCO** dialyzer HD (see Table 2), which plateaued and remained unchanged throughout the intervention period. However, levels of both FLC significantly increased following cessation of HD with the **MCO** dialyzer during the wash-out of high-flux HD phase. (see Table 2). The rebound supports the hypothesis that this dialyzer can result in sustained reduction in middle molecules. The ability to provide sustained removal of large middle molecules such as lambda FLC (45 kDa) suggests that **MCO** dialyzer HD is a promising therapy to enhance removal of other large middle molecules such as soluble tumor necrosis factor receptor-1 (27-30 kDa[1]), fibroblast growth factor-23 (32 kDa[1]), advanced glycosylated end products (<1-70 kDa[1]) that are not cleared by current conventional HD therapies, but are strongly implicated in chronic inflammation and accelerated cardiovascular disease in patients with ESKD.

	Average change from week 4-6 (95% CI)	*p* value	Average change from week 28-32 (95% CI)	*p* value
Lambda-FLC, mg/L	-9.1 (-14.4 to -3.7)	0.001	7.9 (0.8 to 14.9)	0.03
Kappa-FLC, mg/L	-5.7 (-9.8 to -1.6)	0.007	8.2 (1.3 to 15.1)	0.02

TABLE 2. Change in lamda- and kappa-FLC following the initial exposure (week 4-6) and cessation of MCO dialyzer (week 28-32) respectively. Adapted from Krishnasamy et. al. Abbreviations: CI, confidence interval; FLC, free light chains.

No significant change in β-2 microglobulin was observed for the duration of treatment with **MCO** dialyzer. As standard high-flux HD and HDF provide excellent clearance of β-2 microglobulin, it is not surprising that this study did not find a change in the levels of β-2 microglobulin following conversion to the **MCO** dialyzer HD from standard dialysis treatments.

Adverse Events

There were no reported SAE's related to the **MCO** dialyzer for the entire duration of the study.

Study Limitations

The major limitation of the study was the single-arm design. In addition, post-dialysis serum and dialysate concentrations of albumin and middle molecules were not performed and may have provided more in-depth evidence especially regarding the efficacy of this membrane. Participant-level information on the type of dialysate including citrate-based dialysis buffer that may have an impact on middle molecule removal was not collected during the study period. By design, this study excluded major factors that may impact serum albumin measurements and confound the primary outcome in order to assess the independent effect of **MCO** dialyzer on serum albumin.

CONCLUSIONS

REMOVAL-HD demonstrated that regular use of **MCO** dialyzer for 6 months in chronic HD patients was safe and did not result in a significant fall in serum albumin. This study's results support the hypothesis that albumin loss will not be a limitation of the future application of the **MCO** dialyzer in chronic HD. In addition, the significant rebound of FLC levels following cessation of HD with the **MCO** dialyzer supports the hypothesis that this dialyzer can result in sustained reduction in middle molecules (up to 45 kDa) and represents a promising therapy to enhance removal of other large middle molecules.

REMOVAL-HD study demonstrated MCO dialyzer's effective removal of middle molecules up to 45 kDa, such as lambda-FLC, while maintaining stable serum albumin levels, with only 0.7g/L decline in overall serum concentrations.

References: 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.