Efficacy and Safety of Expanded Hemodialysis with the Theranova 400 Dialyzer: A Randomized Controlled Trial

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BACKGROUND

The loss of kidney function in patients with kidney failure causes accumulation of solutes termed uremic toxins due to their negative impact on patient health. These toxins can be grouped into small molecular weight water-soluble molecules, middle molecules, and protein-bound solutes. While the smaller molecules with a molecular mass < 0.5 kilodaltons (kDa) are effectively removed by dialysis, conventional dialysis has more difficulty in clearing middle molecules ranging from 0.5 to 60 kDa. Middle molecules can be further subdivided into two groups based on their molecular weight: conventional middle molecules of 0.5-25 kDa and larger middle molecules of > 25 kDa. The former group includes β2-microglobulin (11.8 kDa), historically considered the standard representative of a middle molecule, while the latter includes free immunoglobulin light chains including λ free light chains (FLCs) (45 kDa). Larger middle molecules are associated with inflammation, cardiovascular events, and other dialysis-related comorbidities in patients with comorbid cardiovascular disease, mineral and bone disorders, and infectious diseases.

Hemodialysis (HD) removes solutes, including small molecules (< 0.5 kDa) and conventional middle molecules (0.5-25 kDa), primarily by diffusion, with very limited convection. Highly porous membranes, such as those featured in high-flux dialyzers, allow some middle molecules like β2-microglobulin to pass through the membrane, but these membranes do not readily clear larger solutes. Larger middle molecules (> 25 kDa) need to be removed either by convection or by highly permeable membranes.

The term expanded HD has been proposed to define a treatment where diffusion and convection are technically integrated inside a hollow-fiber dialyzer equipped with a medium cut-off membrane, enabling removal of small, conventional middle molecules and large middle molecular uremic toxins. The **Theranova** dialzyer provides expanded hemodialysis using a hollow-fiber single-use dialyzer, with improved removal of large proteins > 25 kDa while selectively maintaining essential proteins such as albumin.

Existing data on the performance of medium cut-off dialyzers are based on short-term, non-randomized clinical trials. In contrast, this study was a randomized, longer-term (6 months) study.

OBJECTIVE

To evaluate the efficacy of **HDx** therapy with the **Theranova** 400 membrane for larger middle molecule removal with acceptable serum albumin loss and safety profile over a 6-month period.

METHODOLOGY

The multicenter open-label, randomized controlled trial was conducted in 21 centers in the US between September 2017 and October 2018.

Participants

Patients receiving 3X/week in-center maintenance hemodialysis, ages 22 years and older, who met the following criteria were included in the study:

- Clinically stable without acute medical events in the past 30 days
- Receiving HD with a high-flux dialyzer for at least 3 months prior
- Expected to maintain an acceptable urea clearance (Kt/V) with a dialyzer of an approximate surface area of 1.7 m2
- Stable functioning vascular access

Key exclusion criteria included: history of acute infection ≤ 4 weeks prior to randomization and patients with chronic liver disease, paraprotein-associated disease, hepatitis, HIV, bleeding disorders, active cancer, monoclonal or polyclonal gammopathy. Patients with known serum κ/λ FLC ratio less than 0.37 or greater than 3.1 suggestive of monoclonal plasma diseases were also excluded.

Of 282 patients meeting the inclusion criteria, 172 participants were randomized with 86 in each group.

Methods

The study was an open-label study without concealment of the dialyzer used; the allocation was concealed to the central laboratory and study sponsor. Patients were randomized to receive treatment with either **Theranova** 400 dialyzer (Vantive Healthcare International) or Elisio-17H (Nipro Corporation). Randomization to **Theranova** 400 dialyzer or Elisio-17H, a similar surface area high-flux dialyzer (1.7 m2), was stratified by site with dynamic allocation. Dialysis prescription and management were performed per institutional practice. Monthly microbiological water/dialysate quality testing according to current Centers for Medicare and Medicaid Services regulations for dialysis water and conventional dialysate were required. Hemodialysis treatment duration per session for each individual varied based on clinical requirements determined by the clinician, based on the participants' needs. Medications were administered according to each center's standard practice.

Outcomes

Primary Safety and Efficacy Outcomes

The primary safety endpoint was the level of pre-dialysis serum albumin (65 kDa)[1] measured after 24 weeks of treatment, and the primary efficacy endpoint was the removal of λFLCs (45 kDa) measured at 24 weeks of treatment expressed as a reduction ratio (RR).

Secondary Safety and Efficacy Outcomes

Secondary safety endpoints were change in serum albumin from baseline at weeks 4 and 8.

Secondary efficacy endpoints included the RRs of λ FLCs at 4 weeks and other middle to large molecules: complement

factor D (24 kDa); Symbol FLC (23 kDa); interleukin 6 (IL-6) (25 kDa); tumor necrosis factor alpha (TNFα) (17 kDa); and β2-microglobulin (11.8 kDa) at 4 weeks and at 24 weeks of treatment. Single pool Kt/V was also assessed.

Adverse Outcomes
Adverse events were monitored through study completion.

Exploratory Outcomes
Exploratory endpoints consisted of patient reported quality of life using the Kidney Disease Quality of Life (KDQoL-36) instrument and the EuroQol (EQ-5D-5L) instrument as well as inflammation assessment by highly sensitive C-reactive protein (hsCRP).

RESULTS

Patient Population

Twenty-one centers participated in this clinical study. Of 282 patients meeting the inclusion criteria, 172 participants were randomized, with 86 in each group. A total of 130 participants completed the study; 65 in the **Theranova** 400 dialyzer group; 65 in the Elisio-17H group. Sensitivity analyses via multiple imputation and last observation carried forward for participants who did not complete the study demonstrated similar results to participants who completed the study.

Safety Outcomes

Primary Safety Outcome
At baseline, the mean pre-dialysis level of serum albumin in the **Theranova** 400 dialyzer group (4.0 ± 0.3 g/dL) was comparable to the Elisio-17H group (4.0 ± 0.3 g/dL). Likewise, after 24 weeks of treatment, the mean pre-dialysis serum albumin level was 4.0 ± 0.3 g/dL in the **Theranova** 400 dialyzer group and 4.1 ± 0.4 g/dL in the Elisio-17H group, demonstrating non-inferiority of **Theranova** 400* dialyzer in maintaining serum albumin levels. See Table 1.

Parameter	Dialyzer	n	Mean (SD)	Median	Min, Max	Two-Sided 95% Confidence Interval*
Pre-dialysis serum albumin after 24 weeks (g/dL)	**Theranova** 400	64	4.0 (0.3)	4.0	3.5, 4.7	-0.12 to 0.05
	Control	65	4.1 (0.4)	4.0	3.2, 4.9	

TABLE 1. Primary Safety Outcome: Pre-dialysis Serum Albumin Assessment after 24 Weeks. Abbreviations: SD: standard deviation. Table adapted from Weiner et al.*If the lower bound of the two-sided 95% confidence interval around the mean estimated treatment difference between **Theranova** 400 dialyzer and the control is > -0.1765 then non-inferiority can be claimed. If the lower bound of the two-sided 95% confidence interval is > 0, then superiority may be concluded.

Secondary Safety Outcomes
The change in serum albumin from baseline was significantly different between the two groups only after weeks 4 and 8. After week 4, the mean level was 4.0 ± 0.3 g/dL with a -0.1 ± 0.2 mean change from baseline in the **Theranova** 400 dialyzer group, whereas in the Elisio-17H group, the mean level was 4.0 ± 0.3 with a 0.0 ± 0.2 mean change from baseline (p=0.03). After week 8, the mean level was 3.9 ± 0.3 g/dL with a -0.1 ± 0.3 mean change from baseline in the **Theranova** 400 dialyzer group, whereas in the Elisio-17H group, the mean level was 4.0 ± 0.3 g/dL with a 0.0 ± 0.2 mean change from baseline (p=0.004). Although the differences in change from baseline between the two groups after weeks 4 and 8 were statistically significant, the observed changes were well below 5%, and the mean levels were still within normal lab ranges. See Table 2.

Efficacy Outcomes

Primary Efficacy Outcome
Theranova 400 dialyzer showed significantly larger removal of λ FLCs at 24 weeks of treatment than the Elisio-17H dialyzer (mean RR of 33% ± 11.0% vs 17% ±13% at 24 weeks [p <0.001]. Significantly larger removal of λ FLC was also observed with the **Theranova** 400 dialyzer at 4 weeks of treatment than with the Elisio-17H dialyzer (mean RR of 39% ± 14% vs 20% ± 11% [p <0.001]). See Table 3, Figure 1.

Secondary Efficacy Outcomes
Theranova 400 dialyzer demonstrated superior removal of middle to large molecules as demonstrated by reduction ratios measured at 4 and 24 weeks: complement factor D, κ FLCs, TNFα, and β2-microglobulin (p <0.001 for all).The level of IL-6 at the end of the study was lower than at the start of treatment for the **Theranova** 400 dialyzer group. The RR of IL-6 was negative for the control at both 4 (5% ± 46% vs -9% ± 61%; p=0.09) and 24 weeks of treatment (11% ± 38% vs -3% ± 39%; p=0.05); these differences were not statistically significant. See Table 3, Figure 1.

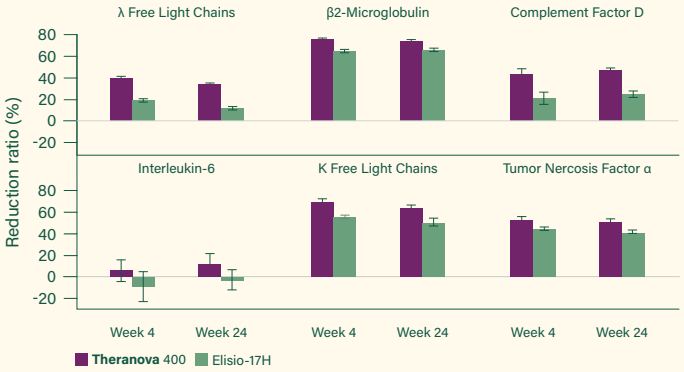

FIGURE 1. Reduction ratios of middle molecules at 4 weeks and 24 weeks. Adapted from Weiner et al.

Single pool Kt/V was assessed after every 4 weeks of treatment. There were no significant differences in the mean single pool (sp) Kt/V values at all measured time points, except for week 8, where the spKt/V for **Theranova** 400 dialyzer was 1.62 ± 0.29 and the value for the Elisio-17H was 1.51 ± 0.32 (p=0.02). The value of spKt/V was within adequacy standards at all measured time points.

Adverse Outcomes

No significant differences were observed between the **Theranova** 400 dialyzer and the Elisio-17H groups in incidence

Parameter	Timepoint	Theranova 400					Control					
		(n)	Mean (SD)	Median	Min, Max	95% Confidence Interval	(n)	Mean (SD)	Median	Min, Max	95% Confidence Interval	p-value
Pre-dialysis serum albumin (g/dL)	Baseline	86	4.0 (0.3)	4.0	3.4, 4.9	NA	86	4.0(0.3)	4.0	3.3, 4.7	NA	NA
Change in pre-dialysis serum albumin from baseline (g/dL)	4 weeks	80	-0.1 (0.2)	-0.1	-0.8, 0.6	-0.14 to -0.03	77	0.0 (0.2)	0.0	-0.7, 0.5	-0.04 to 0.05	0.03
	8 weeks	78	-0.1 (0.3)	-0.1	-0.8, 0.5	-0.17 to -0.05	77	0.0 (0.2)	0.0	-0.6, 0.5	-0.05 to 0.05	0.004
	12 weeks	77	-0.1 (0.3)	-0.1	-1.2, 0.6	-0.19 to -0.06	72	-0.0 (0.2)	0.0	-0.8, 0.5	-0.10 to 0.01	0.13
	16 weeks	72	-0.1 (0.3)	-0.1	-1.3, 0.7	-0.21 to -0.05	71	-0.0 (0.3)	0.0	-1.6, 0.5	-0.10 to 0.05	0.11
	20 weeks	66	-0.1 (0.3)	-0.1	-0.7, 0.5	-0.15 to -0.02	69	0.0 (0.3)	0.0	-0.9, 0.5	-0.05, to 0.08	0.07
	24 weeks	64	0.0 (0.3)	0.0	-0.6, 0.4	-0.06 to 0.07	65	0.0 (0.3)	0.1	-0.6, 0.8	-0.02 to 0.11	0.61

TABLE 2. Secondary Safety Outcomes: Baseline and Change from Baseline of Pre-dialysis Serum Albumin. Abbreviations: SD: standard deviation. Table adapted from Weiner et al.

Parameter	Dialyzer	Week 4 (n)	Mean (SD)	Median	Min, Max	p-value	Week 24(n)	Mean (SD)	Median	Min, Max	p value
Primary Efficacy Outcome											
RR of λ FLCs* (45 kDa)	**Theranova** 400	80	39.3 (14.5)	42.4	-46.2, 71.1	-<0.001	63	33.3 (11.0]	32.8	8.1, 54.1	<0.001
	Control	75	19.9 (11.4)	18.9	-4.5, 41.6		65	17.2 (12.9)	15.9	-10.7, 74.2	
Secondary Efficacy Outcomes											
RR of complement factor D (24 kDa)	**Theranova** 400	83	43.0 (23.9)	48.0	-58.1, 78.5	<0.001	62	45.0 (10.4)	46.0	11.0, 68.0	<0.001
	Control	76	20.9 (23.7)	22.5	-110.9, 77.8		65	23.6 (12.1)	23.9	-47.0, 45.5	
RR of λ FLC (23 kDa)	**Theranova** 400	80	68.8 (17.3)	72.1	-57.9, 94.6	<0.001	63	63.8 (11.8)	65.8	27.8, 87.4	<0.001
	Control	75	54.8 (14.5)	56.0	-29.1, 77.6		65	50.0 (13.2)	49.4	2.3, 74.1	
RR of IL-6 (25 kDa)	**Theranova** 400	80	5.5 (45.9)	19.6	-155.4, 66.1	0.09	63	11.0 (37.8)	20.8	-128.5, 66.2	0.05
	Control	78	-9.2 (60.6)	3.9	-341.2, 55.6		65	-2.6 (39.4)	7.8	-162.2, 46.2	
RRof TNFα (17 kDa)	**Theranova** 400	80	52.5 (9.4)	54.3	16.3, 72.4	<0.001	63	50.7 (9.3)	52.2	23.8, 68.5	<0.001
	Control	78	44.1 (9.3)	45.3	11.0, 58.1		65	41.5 (10.2)	41.9	-0.9, 57.9	
RR of β2-microglobulin (11.8 kDa)	**Theranova** 400	78	75.7 (8.2)	77.2	46.6, 98.9	<0.001	63	73.6 (10.4)	75.9	30.3, 96.7	<0.001
	Control	76	64.9 (8.9)	65.6	24.1, 83.2		65	65.4 (9.4)	65.9	36.8, 90.0	

TABLE 3. Primary and Secondary Efficacy Outcomes: Reduction Ratios (RR) (%) of Middle Molecules at 4 Weeks and 24 Weeks.

*The reduction ratio of λ free light chains at 4 weeks of treatment was a secondary efficacy outcome. Abbreviations. RR: reduction ratio; FLC: free light chain. Table adapted from Weiner et al.

(p=0.87) and incidence rate (p=0.32) of adverse events (AEs). There were 19 serious adverse events (SAEs) in 15 participants in the **Theranova** 400 dialyzer group, and 39 SAEs in 23 participants in the Elisio-17H group. This difference was not statistically significant. There were no SAEs associated with either device. None of the AEs were unanticipated; all were AEs typically seen in maintenance HD patients. Six patients died during the study, 3 in each group, with 1 death in the Elisio-17H group occurring after participant withdrawal from the study. None of the deaths were assessed as related to either device.

Exploratory Outcomes

There were no significant differences in the mean hs-CRP at all trial time points. Additionally, no significant differences were observed in the KDQOL-36 survey and EQ-5D-5L questionnaire results between the two groups.

Strengths & Limitations

Study limitations included conservative exclusion criteria and associated high screening failure rates, study completion rate, insufficient sample size/duration to comment on clinical outcomes such as cardiovascular events and mortality.

The trial had multiple strengths, including the randomized design and longer length of study (6 months) vs previous studies, high rates of adherence with minimal loss to follow-up and consistent results across solutes analyzed.

DISCUSSION AND CONCLUSIONS

Multiple middle molecules are present at higher levels in dialysis patients and have been associated with adverse outcomes. Specifically, larger middle molecules are associated with inflammation, cardiovascular events, and other dialysis-related comorbidities in patients with comorbid cardiovascular disease, mineral and bone disorders, and infectious diseases. In this study, **Theranova** 400 dialyzer showed significantly greater (p <0.001) removal of conventional and larger middle molecules λ FLC (45 kDa), complement factor D (24kDa), λ FLC (23 kDa), TNF-α (17 kDa), and β-2 microglobulin (11.8 kDa) than Elisio 17-H at 4 weeks and 24 weeks. In parallel, no sustained reduction was seen in serum albumin levels (65 kDa), an important finding with the association between higher serum albumin concentration and better outcomes in hemodialysis patients. Given the potential role of these uremic toxins in cardiovascular disease and inflammation in kidney failure patients, newer technologies enhancing clearance of middle molecules while limiting loss of important proteins such as albumin may have an important role in improving health of dialysis patients.

Study results suggest that there may be a role for **HDx** therapy to improve clinical outcomes. In this trial, λ FLCs (45 kDa) were studied as a representative large middle molecule that is easily measured rather than as a presumptive 'uremic toxin', with the current study critically focusing on both clearance of these molecules as well as pre-dialysis levels of large middle molecules. The latter is notable; if there is toxicity associated with retained uremic solutes, therapeutic management will require sustained reduction in the levels of these solutes.

In conclusion, primary and secondary endpoints for safety and efficacy were met. **HDx** therapy with the **Theranova** 400 dialyzer is safe and efficacious, providing superior removal of larger middle molecules including several putative uremic toxins as compared to a similar size high-flux dialyzer while maintaining serum albumin. While this study demonstrated greater removal of large middle molecules among prevalent hemodialysis patients, larger studies of longer duration are needed to assess long term potential beneficial effects related to more effective removal of these middle molecules, including improvements in cardiovascular disease, inflammation, mortality, and key patient-reported outcomes.

The Theranova dialyzer provides significant and superior removal of larger middle molecules while retaining stable albumin levels.

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.