ORIGINAL ARTICLE

A pilot study comparing the efficiency of a novel asymmetric cellulose triacetate (ATA) dialyser membrane (Solacea-190H) to a standard high flux polysulfone dialyser membrane (FX-80) in the setting of extended hours haemodialysis

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Abstract

Aim: To compare small, middle and large-middle molecule clearance; and expression of markers of inflammation, between Solacea-190H (asymmetric cellulose triacetate [ATA]) and FX-80 dialysers in long-hour haemodialysis patients.

Methods: This pilot, randomized cross-over trial recruited 10 home haemodialysis patients. The total study duration was 8 weeks, using each dialyser for 4 weeks. Removal of small (urea, phosphate, creatinine and indoxyl sulfate [IS]), middle and large-middle molecules (beta-2 microglobulin [β2M], albumin), markers of inflammation (interleukin-6 [IL-6], malondialdehyde-modified low density lipoprotein [MDA-LDL] and alpha-1 microglobulin [α1M]), was evaluated in serum and dialysate samples.

Results: Reduction ratios [RR] were calculated for variables at the fourth week of each dialyzer sequence and results expressed as difference in mean RR between dialyzers. There was no difference in clearance of small molecules, with difference in mean RR for urea −2.43 (95% CI -6.44, 1.57; $p = .19$), creatinine −1.82 (95% CI -5.50, 1.85; $p = .28$) and phosphate −2.61 (95% CI −12.45, 7.23; $p = .55$); clearance of middle and large-middle molecules with difference in mean RR (range) for β2M 2.2 (95% CI −3.2, 7.7; $p = .35$), IS 1.8 (95% CI −9.5, 13; $p = .72$) and albumin −0.6 (95% CI −5.5, 4.2; $p = .77$). There was lack of induction of markers of inflammation, including IL-6 15.2 (95% CI −31.9, 62.2; $p = .47$), MDA-LDL −8.1 (95% CI -22.1, 5.8; $p = .21$) and α1M −3.50 (95% CI −29.2, 22.2; $p = .76$). Dialysate removal results were concurrent.

Conclusion: This study showed no difference in clearance of small, middle and large-middle molecules, nor expression of markers of inflammation between dialyzers.

SUMMARY AT A GLANCE

This pilot cross-over randomized controlled trial compares small, middle and large-middle molecule clearance between Solacea-190H (asymmetric cellulose triacetate [ATA]) and FX-80 dialysers in 10 patients using long-hour haemodialysis over an 8-week period, and showed no difference in clearance between the two dialysers.

1 | INTRODUCTION

End stage kidney disease (ESKD) is associated with a myriad of symptoms and acceleration of disease states in multiple organ systems. As a consequence, ESKD cohorts have increased morbidity and mortality, in particular cardiovascular disease (CVD), compared to age-matched cohorts. The accumulation of uraemic toxins and molecules may play a role in the accelerated atherosclerosis and increased CVD risk in ESKD. These have been variably associated with increased inflammation and oxidative stress.[1] Middle and large-middle molecules, such as IL-6, a cytokine and marker of inflammation, have been implicated in the development of cardiovascular disease and associated with increased mortality.[2] Haemodialysis [HD] is the most prevalent type of renal replacement therapy for patients with ESKD. This consists of the removal of water and solutes across a semi-permeable membrane, through a combination of diffusion, convection, adsorption and ultrafiltration.[3] The increased removal of these molecules or strategies to reduce their expression are of great interest in HD cohorts.

A new generation of dialyser membranes, made from ATA, such as the Solacea-190H (manufactured by Nipro Corporation, Japan) claim to possess superior middle and large-middle molecule (>15 kD) clearance in comparison to commonly used high-flux polysulfone dialyser membranes, such as FX-80 (manufactured by Fresenius Medical Care, Germany). These membranes are also stated to have lower levels of protein adsorption[4] and less performance degradation over the duration of a dialysis session,[5,6] which clinically, may lead to reduced albumin loss and improved biocompatibility. Biocompatibility relates to the induction of complement activation and other inflammatory molecules upon contact of blood elements with the dialysis circuit.[2,7] Improvements in biocompatibility may reduce the prevalence of long term sequelae seen in dialysis patients such as chronic inflammation, relative immunodeficiency and an overall poor nutritional state, which is also mediated by albumin loss.[3,8,9]

Our pilot study aimed to compare small (urea, phosphate, creatinine and IS), middle and large-middle molecule (β2M, albumin) clearance as well expression of markers of inflammation (IL-6, MDA-LDL and α1M), between the ATA dialysis membrane (Solacea 190-H) and a commonly used polysulfone dialysis membrane (FX-80). We hypothesised that solute clearance was likely to be similar between the two dialysers.

2 | METHODS

2.1 | Study participants

Patients were selected from the cohort of existing home haemodialysis patients at Monash Health and were eligible for inclusion if they underwent nocturnal sessions which were at least 7 h in duration on alternate days, through an established arteriovenous fistula, and signed an informed consent form.

Patients were excluded if they had a hospital admission for any reason (including infection), or a cardiovascular or cerebrovascular event during the preceding 3 months. Exclusion criteria also comprised concerns around medical or psychological instability and if living donor transplantation was planned within the upcoming 4-month period.

2.2 | Study design

This pilot study had a prospective, randomized crossover design with a duration spanning 8 weeks in total (Figure 1). Participants were assigned to either the Fresenius FX-80 or Solacea-190H dialyser for a 4-week period, whilst dialysing at home. Both membranes are highly porous, high flux membranes. The FX-80 is a polysulfone membrane with a surface area of 1.8 m^2, KUF (ultrafiltration coefficient) of 53 mL/h/mmHg and stated clearance for urea 276 mL/min (clearance under the conditions of QB = 300 mL/min, QD = 500 mL/min QF = 0 mL/min). By comparison, the Solacea-190H dialyser has a surface area 1.9 m^2, KUF of 72 mL/h/mmHg and stated clearance for urea 278 mL/min (clearance under the conditions of QB = 300 mL/min, QD = 500 mL/min QF = 10 mL/min).

The dialyser sequence was determined by randomisation and performed by a study investigator who was not involved in recruitment of participants. No changes to chronic dialysis prescriptions were made for the duration of the study, with the exception of dialyser type. Blood flow rate (Qb) was 250 mL/min and dialysate flow rate (Qd) 300 mL/min. Dialysate composition was sodium 138 mEq/L, potassium 2 mEq/L, bicarbonate 35 mEq/L and calcium 1.25 mEq/L. Anticoagulation on dialysis was with intravenous enoxaparin.

The removal of a number of small to middle range molecules, as well as indices of biocompatibility were evaluated, using timed

FIGURE 1 Study protocol
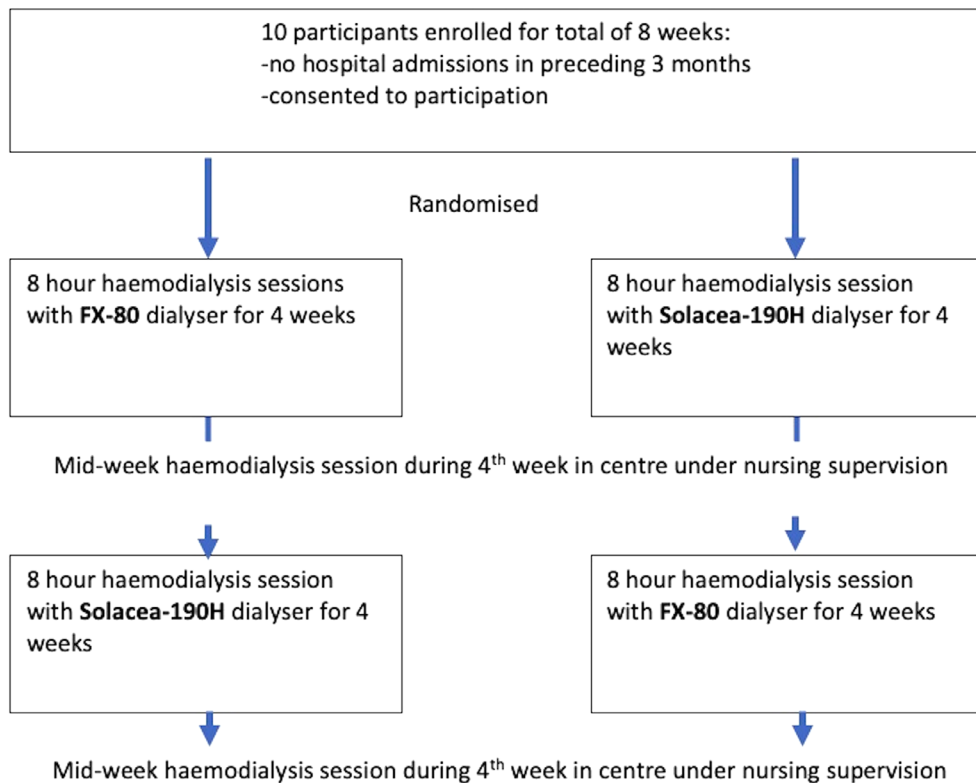
collection of blood samples obtained during the mid-week session of the 4th week, which was 8 h in duration. Patients were required to attend the home haemodialysis training unit for this test-session. At the end of this 4-week block, there was crossover to the second dialyser type.

This study was approved by the Monash Health Research and Ethics Committee–approval number HREC/51556/MonH-2019-166 657 and registered as a clinical trial in the Australian New Zealand Clinical Trials Registry (ACTRN12619000424101).

2.3 | Study outcomes and measurements

Serum samples were obtained pre- and post-dialysis (collected 2 min following cessation of the blood pump) from the arterial line and sent to Monash Pathology for analysis of biochemical parameters including urea, creatinine, phosphate, albumin and β2M. Partial dialysate collections were used to calculate total dialysate, as previously described[10] and analysed for urea, phosphate, creatinine, β2M, IS, albumin and α1M removal.

Additional plasma and serum samples were stored in a −80°C freezer for batched measurement of additional study factors by enzyme-linked immunosorbent assays (ELISA), at the research laboratory within the Department of Nephrology at Monash Health. Samples were analysed as per the manufacturer's protocols for total, as opposed to free IS using the enzyme method (human kit supplied by Nipro Corporation, Osaka, Japan), as outlined in Abe et al.[11] This study found the enzyme method for measuring total IS was

accurate, repeatable and correlated well with HPLC measurements. Manufacturer's protocols were also applied for measurement of IL-6 (AB46027, Abcam Australia), MDA-LDL (10-1143-01, human oxidized LDL kit, Mercodia, Uppsala, Sweden) and α1M (Human Alpha-1-Microglobulin ELISA Kit AB22689 Abcam UK, for plasma; and Human alpha-1 microglobulin ELISA Kit AB108884, Abcam UK, for dialysate). The post-dialysis values for molecules greater than MW 5000 were corrected for haemoconcentration, or contraction of circulatory blood volume during dialysis, according to the following formula proposed by Bergstrom and Wehle[12]:

$$\text{uncorrected post dialysis value} \left/ \left[\frac{1 + \Delta \text{body weight}}{0.2 \times \text{post dialysis body weight}} \right] \right.$$

Routine clinical parameters (pre and post-dialysis weight, serial blood pressures and ultrafiltration volumes), were also recorded during the supervised session.

2.4 | Statistical analysis

Baseline descriptive data are presented as means (± SD). Reduction ratios (RR) were calculated based on pre (T0) and post (T480) dialysis results for each study variable, using the formula RR (%) = [1 − (T0/T480)] × 100. The difference in the mean RR was compared between the study dialysers using paired t-tests, accounting for the cross-over design of the study. Results are expressed as a mean difference compared to the FX 80 dialyser. All results are considered

statistically significant where the *p*-value is less than .05. All analyses were conducted using Stata MP 15.1 (Statacorp, College Station, TX, USA).

3 | RESULTS

3.1 | Characteristics of participants

Potentially suitable patients were identified by nursing staff in the home haemodialysis unit based on dialysis duration and the inclusion criteria. Of the 14 patients approached for participation, three declined to participate due to personal preference and one patient withdrew following randomisation, prior to commencing the trial, due to time constraints.

Amongst the 10 participants who did consent, there was a male preponderance, with a mean age of 50.9 (± 9.2) years and dialysis vintage of 63 (± 36) months. All participants had an established arteriovenous fistula and the aetiology of ESKD varied. These characteristics are further detailed in Tables 1 and 2.

3.2 | Small molecules

The mean RR for are outlined in Table 3. When the difference in mean RR for small molecules were compared, the results were not significant, with a RR of −2.43 (95% CI −6.44, 1.57; *p* = .19), −1.82 (95% CI −5.50, 1.85; *p* = .28), −2.61 for (95% CI −12.45, 7.23; *p* = .55) and 1.8 (95% CI −9.5, 13; *p* = .72), for urea, creatinine, phosphate and IS, respectively.

3.3 | Middle/large-middle molecules and markers of inflammation

Pre-dialysis values and mean reduction ratios for albumin, β2M, IL-6, α1M and MDA-LDL for FX80 and Solacea 190H are listed in Tables 4 and 5. The differences in mean RR for these molecules were not statistically significant, at albumin −0.6 (95% CI −5.5, 4.2; *p* = .77), β2M 2.2 (95% CI −3.2, 7.7; *p* = .35), IL-6 15.2 (95% CI −31.9, 62.2; *p* = .47), α1M -3.5 (95% CI −29.2, 22.2, *p* = .76) and MDA-LDL −8.1 (95% CI −22.1, 5.8; *p* = .21).

3.4 | Dialysate removal

The removal of some molecules in dialysate was also measured. Mean dialysate removal (range) for urea was 775.6 mmol/session (292.8–1470) and 909.2 mmol/session (436.5–1465); creatinine 20222.6 μmol/session (9198–44 545) and 25735.1 μmol/session (12513–49 392) for the FX-80 and Solacea membranes, respectively. For β2M 279.1 mg/session (94.6–516.3) and 287.3 mg/session (120–450.7); α1M 195.6 mg/session (92.6–331)

TABLE 1 Baseline characteristics of study participants

Demographic variable	Mean ± SD
Age (years)	50.9 ± 9.2
Gender (male)	8
Dialysis vintage (months)	63.3 ± 36
Target weight (kg)	107.4 ± 32
Vascular access:	
AVF	10
Aetiology of ESKD:	
Diabetic nephropathy	2
IgA nephropathy	2
Lupus nephritis	1
Glomerulonephritis secondary to ANCA-associated vasculitis	3
Undifferentiated glomerulonephritis	1
Polycystic kidney disease	1
Dialysis session parameters	
Hours	8
Blood flow rate (mL/min)	250
Dialysate flow rate (mL/min)	300
Haematological parameters at baseline	
Haemoglobin (g/L)	116 (18)
Platelet count ($\times 10^9$/L)	239 (71)
Biochemical parameters at baseline	
Creatinine (μmol/L)	825 ± 251
Urea (mmol/L)	18 ± 5
Phosphate (mmol/L)	2 ± 0.6
Beta-2 microglobulin (mg/L)	35 ± 6
Albumin (g/L)	36 ± 2
Indoxyl sulfate (μmol/L)	148 ± 81
Markers of inflammation at baseline	
IL-6 (pg/mL)	9 ± 9
MDA-LDL (mU/L)	11 ± 2

TABLE 2 Clinical data for study participants

Clinical characteristic	FX80 Mean ± SD	Solacea-190H Mean ± SD
Pre-dialysis systolic blood pressure (mmHg)	143 (± 16.6)	148 (± 14.9)
Post-dialysis systolic blood pressure (mmHg)	132 (± 10.6)	128 (± 11.7)
Ultrafiltration volume (L)	2.3 (± 0.9)	2.5 (± 0.7)

and 500.6 mg/session (309.1–609.6). The values for IS, phosphate and albumin were below the limit of detection for the assays used and these results are therefore not reported. The remaining values, as well as the difference in mean, are summarized in Table 6; the only statistically significant result was for the mean difference

TABLE 3 Reduction ratios in serum samples, for small molecules with FX-80 and Solacea-190H dialyser membranes and corresponding difference in means

	FX80 mean reduction ratio	Solacea-190H mean reduction ratio	Difference in mean (95% CI)	*p*-value
Small molecules:				
Urea	76.2 (± 5)	78.2 (± 5)	−2.43 (−6.44, 1.57)	.19
Creatinine	68.9 (± 4)	70.3 (± 4)	−1.82 (−5.50, 1.85)	.28
Phosphate	51.4 (± 13)	52.1 (± 14)	−2.61 (−12.45, 7.23)	.55
IS	41.0 (±10)	39.9 (±12)	1.8 (−9.5, 13)	.72

TABLE 4 Serum concentrations of albumin and markers of inflammation with FX-80 and Solacea-190H dialyser membranes

	FX 80 Mean ± SD	Solacea-190H Mean ± SD
Pre-dialysis IL-6 (pg/mL)	7.7 (±8)	8.9 (±10)
Pre-dialysis MDA-LDL (mU/L)	9.8 (±3)	11 (±2)
Pre-dialysis alpha-1 microglobulin (μg/mL)	92.9 (±48)	89.3 (±41)
Pre-dialysis albumin (g/L)	34.4 (±3)	35.1 (±3)
Post-dialysis albumin (g/L)	34.1 (±5)	34.8 (±4)

TABLE 5 Mean reduction ratios (%) for middle and large-middle molecules and markers of inflammation/oxidative stress in serum samples, with FX-80 and Solacea-190H dialyser membranes, adjusted for haemoconcentration

Mean reduction ratio (range)	FX80	Solacea 19	Difference in mean (95% CI)	*p*-value
β2M	75.1 (66.6–84.6)	71.9 (58.1–81.6)	2.2 (−3.2, 7.7)	.35
Albumin	9.16 (0.80–16.5)	9.1 (2.13–15.06)	−0.6 (−5.5,4.2)	.77
α1M	−2.41 (− 94.5–55.4)	0.17 (− 42.4–33.3)	−3.5 (−29.2, 22.2)	.76
IL-6	25.0 (− 45.1–76.2)	12.7 (− 54.3–69.6)	15.2 (−31.9, 62.2)	.47
MDA-LDL	4.51 (− 20–30.0)	13.2 (− 1.85–24.9)	−8.1 (−22.1, 5.8)	.21

TABLE 6 Mean dialysate removal for middle and large-middle molecules and markers of inflammation/oxidative stress with FX-80 and Solacea-190H dialyser membranes

Mean dialysate removal (range)	FX80	Solacea 19H	Difference in mean (95% CI)	*p*-value
Urea (mmol)	775.6 (292.8–1470)	909.2 (436.5–1465)	−82.5 (−472.9, 308.0)	.63
Creatinine (μmol)	20222.6 (9198–44 545)	25735.1 (12513–49 392)	−4496.878 (−10590.71596.9)	.12
β2M (mg)	279.1 (94.6–516.3)	287.3 (120–450.7)	0.8112501 (−77.9, 79.5)	.98
α1M (mg)	195.6 (92.6–331)	500.6 (309.1–609.6)	−304.9 (−402.5, −207.2)	<.05

between dialyser membranes for α1M −304.9 (95% CI −402.5, −207.2, *p* < .05).

3.5 | Adverse events

One participant was unable to complete the study due to recurrent clotting of dialysis lines whilst using the Solacea-190H dialyser, despite there being no change to routine anticoagulation on dialysis. This resulted in withdrawal from the study and a change back to the FX-80 dialyser, in the interests of patient safety. No other adverse events were reported.

4 | DISCUSSION

Our study comparing the FX-80 and Solacea-190H dialysers demonstrated excellent performance by both dialysers, as evidenced by the clearance of small, middle and middle-large sized molecules. This was an expected finding given the long-hours HD setting and the operating characteristics of modern high flux dialysers. Interestingly, there was no appreciable difference in albumin loss, or biocompatibility, using markers of inflammation as a surrogate measure.

β2M (MW 11800 Da) is the archetypal middle-molecule, the removal of which was specifically targeted with the development of high-flux dialysers. It is considered pro-inflammatory and has been

identified as an independent risk factor for cardiovascular disease, irrespective of severity of chronic kidney disease.[13] IS (MW 213 Da) is a small, protein bound uraemic toxin, implicated in endothelial and vascular dysfunction.[14] This study demonstrated no difference in the mean RR for either molecule. This is consistent with other studies which also evaluated IS and β2M clearance with variable dialysis frequency, dialyser size, blood and dialysate flows; to find there was minimal effect of these parameters on clearance.[14–16]

The SAFE study[17] is a two-arm open-label crossover study, which evaluated the use of anticoagulation with an ATA dialyser membrane. Our study did not assess this aspect, in particular, however, the adverse event pertaining to recurrent clotting in one patient appears to be out of keeping with the SAFE study's findings, where a lower propensity towards clotting was noted with ATA dialysers. The RRs obtained as part of the secondary outcomes in their study for urea and β2M with ATA dialysers were comparable to our data, however, the reported RR for IS was higher in their study (45% with citrate and 46% with predilution haemodiafiltration) compared to ours (39%).

A study conducted by Kim et al[6] also compared a high flux polysulfone and polyethersulfone to an ATA dialyser, to find the latter performed superiorly with regards to solute removal, and had lower levels of performance degradation upon exposure to serum. Whilst the Solacea-190H dialyser may have better degradation parameters in a 4 h dialysis session,[6] these differences were not apparent over an 8 h dialysis session, suggesting that the extent of degradation is similar over extended hours. Of note, this particular study was conducted using a single simulated dialysis session with bovine serum. This makes any direct comparison to this study (undertaken during real time haemodialysis sessions, in patients who had multiple exposures to each dialyser) challenging.

The loss of albumin (66 kDA) was found to be negligible in our study. Although this was hypothesised, it was nonetheless an important finding, given that low serum albumin levels are not only a marker of protein catabolism and malnutrition in the haemodialysis population, but a strong predictor of mortality.[18] There are two factors which may be contributing to the small positive RR for albumin in our case, including correction of the post-dialysis bloods for haemoconcentration; and a small, true loss of albumin across the membrane, which we believe occurs, especially in prolonged treatments, as used in this study.

IL-6, a cytokine (MW 21 kDa) and marker of inflammation, was selected for evaluation in this study, as it is commonly present in high circulating levels in dialysis dependent patients. It is implicated in the chronic inflammatory state, protein catabolism and low muscle mass frequently observed in ESKD cohorts.[19,20] It may also play a role in the pathophysiology of left ventricular hypertrophy and systolic dysfunction.[3] In this study, there was no difference in IL-6 expression or induction when comparing the two membranes. α1M (MW 33 kDa) is a marker of inflammation, thought to inhibit leukocyte migration, chemotaxis and IL-2 production when present at high levels as seen in ESKD cohorts.[3] Again, there was no difference appreciable between its measure levels between the two dialyser membranes. MDA-LDL (MW 1 MDa) is a marker of oxidative stress and thought to contribute

to cardiovascular disease.[21] The negligible change in levels of these molecules during the course of a haemodialysis session may potentially indicate that exposure to these particular dialysers fails to stimulate an appreciable inflammatory response. However the marked variability of these results may also relate to non-dialysis factors, specifically, the currently available assays which have not been validated outside of a research setting.

A strength of this study was the randomized crossover design, which reduced any effect of potential confounders. There was also no alteration made to the dialysis prescriptions of participants, and they were permitted to dialyse as usual at home, which likens it more to a "real world" rather than simulated setting. We also evaluated the clearance and expression of markers of inflammation, which are not routinely studied. Although their relevance to clinical outcomes is yet to be fully delineated, this pool of data, particularly as a measure of background expression or long-term expression, may prove useful for future studies to follow. Additionally, we adjusted post dialysis values for middle and large-middle molecules for haemoconcentration. Finally, we measured and confirmed the presence of molecules of interest in this study in dialysate samples. Acknowledging the limitations of the assays used, which are not validated for this purpose, the results appeared to generally concur with serum reduction ratio findings.

One of the key limitations of our study is the small sample size, which restricts its generalisability to the dialysis population at large. Additionally, there was no specified washout period between the two dialysers, which may have a confounding effect on the reduction ratios from the second half of the study period. The 4-week period was selected, as opposed to a shorter period of time, to allow for sufficient stabilization of clinical and biochemical parameters, prior to sampling to minimize this effect. Our study also evaluated the performance of these membranes in the extended hour dialysis setting exclusively, with the intention of maximizing the potential impact of bioincompatibility and membrane degradation. These findings may not be applicable to standard hour haemodialysis, which is the prevalent haemodialysis modality worldwide. This may be especially relevant for the results observed with regards to albumin loss.

A larger randomized controlled trial is warranted to further evaluate these findings pertaining to not only middle and large-middle molecules, but also to add to the body of research on markers of inflammation and oxidative stress. Furthermore, studies are required to ascertain how this translates to patient centred outcomes such as infection and cardiovascular event rates over more extended periods of time, along with safety data in larger cohorts.

5 | CONCLUSION

Our pilot study demonstrated no significant difference in the clearance of small and middle sized molecules or markers of inflammation/oxidative stress between the FX-80 and Solacea-190H dialysers, however, highlights the clinical need for a larger trial to further evaluate these findings.

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