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Protein-Bound Uremic Toxins Removal with Medium Cut-Off Membranes: A Pilot Study Showing No Superiority over High-Flux Dialysis

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Keywords
Medium cut-off membranes · Protein-bound uremic toxins · Advanced glycation end products · Hemodialysis · N-carboxymethyllysine

Abstract

Introduction: Protein-bound uremic toxins such as advanced glycation end products (AGEs) are poorly cleared by conventional dialysis. Medium cut-off (MCO) membranes have been proposed to enhance their removal, but clinical evidence remains limited. ***Methods:*** In this prospective pilot study, 8 maintenance hemodialysis patients were assigned to receive a single dialysis session using either an MCO or high-flux (HF) membrane. Serum levels of N-carboxymethyllysine (CML), soluble receptor for AGEs (sRAGE), and prolactin were measured pre- and post-dialysis. Reduction ratios corrected for hemoconcentration (RRc) were compared between groups. ***Results:*** The median RRc for CML was similar between MCO (36.9%) and HF (35.6%) membranes ($p = 0.686$). sRAGE reduction was lower with MCO membranes (21.8% vs. 41.9%, $p = 0.114$), while prolactin clearance was slightly higher (58.1% vs. 50.9%, $p = 0.486$). No statistically significant differences were observed. ***Conclusion:*** MCO membranes did not demonstrate superior removal of protein-bound toxins compared to HF membranes in this pilot study. These findings highlight the need for alternative strategies, such as adsorption, and larger studies to define the clinical utility of MCO technology.

Introduction

Patients undergoing maintenance hemodialysis (HD) continue to experience elevated cardiovascular morbidity and mortality, mainly attributable to the accumulation of uremic toxins inadequately removed by conventional dialysis techniques [1]. Among these toxins, advanced glycation end products (AGEs) play a key role. AGEs, particularly N-carboxymethyllysine (CML), are pro-oxidant and pro-inflammatory compounds derived from the nonenzymatic glycation of proteins and lipids. Their accumulation is associated with vascular dysfunction, oxidative stress, and chronic inflammation in chronic kidney disease (CKD). Soluble receptor for AGEs (sRAGE), which acts as a decoy receptor mitigating AGE-mediated toxicity, has also garnered attention as a biomarker of endothelial stress [1–3].

Despite high-flux (HF) membranes and online hemodiafiltration, the clearance of protein-bound uremic

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toxins (PBUTs), including AGEs, remains suboptimal. Their protein-binding nature and larger molecular size hinder their effective removal [4, 5]. This limitation has driven the search for novel dialysis strategies aimed at enhancing the elimination of such compounds.

Medium cut-off (MCO) membranes represent a recent innovation in dialysis technology. These membranes are designed with a more uniform and extended pore distribution, allowing improved removal of middle-to large-sized solutes while preserving essential proteins like albumin [6]. Given these characteristics, MCO membranes may offer an advantage in clearing AGEs and other PBUTs, potentially reducing cardiovascular risk in the dialysis population.

Methods

This prospective, single-center, observational pilot study was conducted at the Nephrology and Dialysis Unit of Hospital Carlos Van Buren, Valparaíso, Chile. Eight adult patients undergoing maintenance HD for at least 3 months and without residual renal function were enrolled. Four patients were assigned to receive a single mid-week dialysis session with a MCO membrane and four with a conventional HF membrane.

All sessions lasted 240 min, with a blood flow rate of 350–400 mL/min and dialyzate flow of 500 mL/min. Anticoagulation was achieved using standard unfractionated heparin. Dialyzer used in the HF group was a polyethersulfone/polyvinylpyrrolidone membrane (Clearum™ HS series, Medtronic) characterized by a K_{UF} of 64 mL/h/mm Hg, polypropylene housing free of bisphenol-A, no adsorption properties, and an albumin sieving coefficient of 0.004, while the MCO group utilized membranes with extended cut-off profiles (Theranova®, Baxter).

Blood samples were collected pre- and post-dialysis to determine serum levels of CML, sRAGE, and prolactin. Uremic toxin reduction ratios (RRs) and hemoconcentration-corrected reduction ratios (RRc) were calculated. Correction for hemoconcentration was performed using the following formula [7]:

$$RR_c\,(\%) = 100\ (C_0 - cC_{end})\ /\ C_0$$

where: $cC_{end} = C_{end} / \left(1 + \left[\Delta BW / 0.2\ \left(BW_{post}\right)\right]\right)$; ΔBW = body weight refers to the change in body weight during the treatment, used to account for variations due to ultrafiltration; BW_{post} = represents the body weights after dialysis (kg); C_0 = represents the pre-dialysis plasma concentration of the solute; C_{end} = represents the uncorrected post-dialysis plasma concentration; cC_{end} = represents the hemoconcentration-corrected post-dialysis concentration.

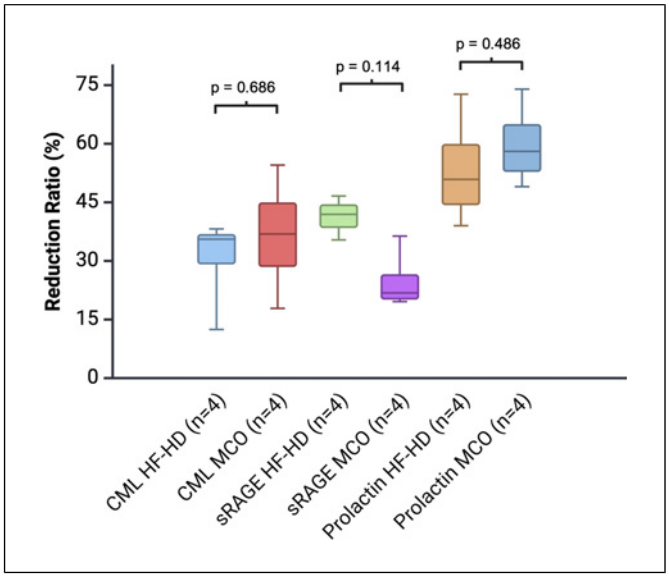

Fig. 1. Hemoconcentration-corrected reduction ratios (RRc%) of uremic toxins after a single dialysis session with high-flux (HF) and medium cut-off (MCO) membranes. Box plots showing hemoconcentration-corrected reduction ratios (RRc%) for N-carboxymethyllysine (CML), soluble receptor for advanced glycation end products (sRAGE), and prolactin after a single dialysis session with either HF hemodialysis (n = 4) and MCO membranes (n = 4). Median CML and prolactin reduction were similar between groups, while sRAGE showed a lower reduction in the MCO group. No statistically significant differences were observed between groups for any solute. Boxes show interquartile ranges (IQR), horizontal lines indicate medians, and whiskers represent minimum and maximum values. RRc was calculated as RRc (%) = 100 × (C0 – cCend)/C0, where cCend accounts for hemoconcentration correction.

Statistical comparisons between groups were performed using the Mann-Whitney U test, with a p value <0.05 considered statistically significant. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Results

The study included 8 patients, evenly divided between the MCO and HF groups. In terms of CKD etiology, the MCO group included 3 patients with stage 5 non-specified CKD and one with IgA nephropathy, whereas all 4 patients in the HF group had stage 5 non-specified CKD. Regarding vascular access, 3 patients in the MCO group used an arteriovenous fistula (AVF) and one a central venous catheter, while all patients in the HF group

used arteriovenous fistulas. Dialysis vintage had a median of 14.5 years [13–17] in the MCO group and 14.5 years [10–23] in the HF group. The median Kt/V was 1.75 [1.53–1.92] in the MCO group and 1.90 [1.75–2.00] in the HF group (p = 0.55). The median ultrafiltration volume per session was 2,600 mL [2,375–2,900] in the MCO group and 2,900 mL [2,000–3,775] in the HF group, without statistically significant differences.

The median hemoconcentration-RRc for CML was 36.89% (interquartile ranges [IQR]: 27.29–47.02) in the MCO group compared to 35.57% (IQR: 19.83–36.15) in the HF group (p = 0.686), with both groups achieving similar toxin removal. For sRAGE, RRc was lower in the MCO group (median 21.81%, IQR: 19.80–26.80) than in the HF group (median 41.93%, IQR: 38.65–44.27) (p = 0.114). In contrast, prolactin showed a higher RRc in the MCO group (median 58.1%, IQR: 51.69–67.87) versus HF (median 50.9%, IQR: 42.69–64.05), also without statistical significance (p = 0.486) (Fig. 1).

Discussion

Our findings suggest that MCO membranes achieve effective removal of PBUTs such as CML and prolactin, comparable to conventional HF membranes. Despite theoretical advantages of MCO membranes in enhancing convective transport and mass transfer of middle to large solutes, the observed removal of CML was not superior to that achieved with HF membranes [6]. This outcome suggests that membrane permeability alone may not overcome the limitations inherent to the removal of tightly protein-bound toxins.

This is consistent with the current understanding that the transfer of protein-bound toxins across the dialysis membrane is strongly influenced by binding affinity and kinetics, limiting their clearance regardless of membrane structure. Thus, while MCO membranes enhance the spectrum of solutes cleared, their effectiveness in removing certain protein-bound compounds may be fundamentally constrained.

Interestingly, the lower reduction of sRAGE with MCO membranes may hold clinical relevance, considering its proposed anti-inflammatory and vasculoprotective role in CKD. Additionally, prolactin removal was slightly higher with MCO, supporting its efficacy in clearing medium-sized molecules.

Recent findings by Koç et al. [8] further highlight the complexity of AGE removal using MCO membranes. In a crossover study of diabetic HD patients, they observed greater reductions in CML and pentosidine with MCO compared to HF dialysis. However, these effects were inconsistently sustained across treatment phases. Our results contrast with these findings, as no superiority of MCO over HF in CML removal was observed, which may reflect differences in patient characteristics, study design, or analytical techniques. Furthermore, the persistent limitations observed with MCO support the need to explore alternative or complementary mass transfer strategies. In this context, hemoadsorption has emerged as a promising adjunct technique. A recent study using the HA130 cartridge demonstrated significantly enhanced CML removal compared to HF dialysis, without affecting protective sRAGE levels. These findings suggest that adsorption-based therapies may offer a more effective route to overcoming the constraints imposed by membrane-based diffusion and convection alone [9, 10].

However, it is important to acknowledge that the lack of statistically significant differences observed in toxin removal may be attributable to the limited sample size and the associated risk of a type II error. Thus, the apparent equivalence between MCO and HF membranes in this context should be interpreted cautiously, as the study may have been underpowered to detect subtle yet clinically relevant differences.

Although statistical significance was not reached for any toxin, the overall safety profile, including the preservation of albumin, supports the feasibility of MCO use in clinical practice. These findings echo prior reports and underscore the need for larger trials assessing not only solute kinetics but also meaningful clinical outcomes.

Conclusion

While MCO membranes are conceptually designed to enhance the removal of middle and larger molecular weight uremic toxins, our findings show that their efficacy in removing protein-bound solutes such as CML is comparable to that of conventional HF membranes. This suggests that overcoming the barriers to effectively removing protein-bound toxins may require approaches beyond membrane permeability alone. The favorable safety profile and a slight advantage in the clearance of middle molecules like prolactin support the continued clinical use of MCO membranes. However, given the limited sample size, these results should be interpreted as hypothesis-generating rather than conclusive. Future studies with larger cohorts and extended treatment durations are needed to validate these findings and clarify the clinical impact of MCO membranes in dialysis care.

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Statement of Ethics

The study protocol was reviewed and approved by the Local Institutional Ethics Committee at Hospital Carlos Van Buren. All procedures were conducted in accordance with the principles of the Declaration of Helsinki and relevant national regulations. Written informed consent was obtained from all participants prior to inclusion. The San Antonio Valparaíso Health Service Ethics Committee approved this study under resolution 002120, Act No. 61.

Conflict of Interest Statement

G.R.-G. has received speaker fees from AstraZeneca, B. Braun, Baxter, Fresenius Medical Care, and Novo Nordisk. C.P.-R. has received honoraria for lectures from Fresenius Medical Care and Medtronic. None of the other authors declare any competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. The authors alone are responsible for the content and writing of this article, responsible for the content and writing of this article.

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Author Contributions

F.A. and G.R.-G. designed the work, G.R.-G., F.A., B.S.-H., C.V., A.R., and C.P.-R. collected and analyzed the data, G.R.-G., F.A., and C.P.-R. drafted the work or substantively revised it, and all authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy and confidentiality agreements with participants but are available from the corresponding author (G.R.-G.) upon reasonable request.

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