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Expanded hemodialysis: a new concept of renal replacement therapy

Jonny Jonny , Maria Teressa

Division of Nephrology, Department of Internal Medicine, Gatot Soebroto Army Hospital, Jakarta, Indonesia

Correspondence to
Dr Maria Teressa, Division of Nephrology, Department of Internal Medicine, Gatot Soebroto Army Hospital, Jakarta 10410, Indonesia; dr.mariateressa@gmail.com

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ABSTRACT

Expanded hemodialysis (HDx) is an innovation that can increase the effectiveness of hemodialysis. The dialysis process is expected to promote more uremic toxins removal without causing significant hypoalbuminemia using the medium cut-off (MCO) membrane or also known as the high retention onset membrane. Compared with conventional membranes such as those of low-flux hemodialysis, high-flux hemodialysis, and hemodiafiltration, the MCO membrane in HDx is considered to be the closest to the physiology of the glomerular membrane. Several studies have shown the use of the MCO membrane in HDx provides clinical benefits and better outcome although further studies are needed to assess the long-term effect and greater impact for dialysis patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Conventional hemodialysis lacks the ability to provide adequate removal of uremic toxins over a broad molecular weight range.
⇒ Retention of wide spectrum of uremic toxins induces adverse biologic effects and various complications.

WHAT THIS STUDY ADDS

⇒ The medium cut-off (MCO) membrane has the potential to remove medium to large molecular weight toxins.
⇒ Routine use of MCO dialyzers is safe and does not cause a significant decline in serum albumin levels.
⇒ The MCO membrane with its expanded hemodialysis (HDx) method has the potential for better removal of toxins and chronic inflammatory factors compared with conventional hemodialysis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ HDx can be an option for dialysis patients who do not achieve maximum results after conventional hemodialysis.

INTRODUCTION

Hemodialysis (HD) technology continues to develop until now, but these developments sometimes achieve unsatisfactory results. One of the unmet needs in HD is the maximum removal of uremic toxin. Currently, the synthetic membrane in HD is not able to remove large uremic toxins, as is done by the glomerular membrane of the kidney. As a result, dialysis patients in their plasma have high moderate to large molecule uremic toxins.[1] Despite technological advances in recent years, HD is still being a burden for patients with chronic kidney disease (CKD).

Currently, HD patients can undergo low-flux HD (LF-HD), high-flux HD (HF-HD), or hemodiafiltration (HDF). The difference between the three techniques lies in the permeability of the dialysis membrane to remove toxins with different molecular weights.[2] LF-HD is conventional HD, having a membrane that is permeable only to toxins with low molecular weight (<1 kD). The HF-HD features a high-flux synthetic membrane which is more biocompatible for removing medium-sized to large-sized molecules, whereas HDF treatment combines diffusive and convective transport with a high-flux membrane.[2 3] Nonetheless, removing medium to large molecules using HF-HD and HDF modes still has limitations. The evolution of HF-HD, also known as protein-leaking membrane (PLM), or super-flux or high cut-off (HCO), can enhance uremic toxin clearance compared with LF-HD but often results in clinically significant hypoalbuminemia. HDF has advantages over other modes, but it is still limited due to higher cost, limitations in infrastructure, and the lack of resources in each dialysis unit.[3]

To increase uremic toxin removal and membrane permeability, in recent years, membrane technologies that have similar efficacy but minimal impact on albumin loss have been developed. The medium cut-off (MCO) membrane or also known as the high retention onset (HRO) membrane, which is now considered as expanded HD (HDx), has led to new hope for the condition and quality of life of HD patients.[4] Thus, this review aims to explore the molecular removal of the dialysis process using the HDx method and its relevance to the clinical benefit for HD patients.

DIALYSIS MEMBRANE EVOLUTION: MCO MEMBRANE

The development of a highly selective and permeable membrane represents a good opportunity for effective and high-quality dialysis. The MCO membrane can not only remove large molecules with a molecular weight of up to 45,000 Da, which is similar in properties to HCO membrane, but can also reduce excessive

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albumin loss as in high-flux membrane.[5] With the development of these membrane characteristics, the use of the MCO membrane expands the spectrum of uremic toxins clearance through HD, hence this new modality is now known as HDx.[4]

MCO membranes have highly selective permeability properties. Boschetti-de-Fierro *et al* conducted an in vitro study regarding the membrane characteristics of dextran filtration and found that the MCO membrane has the most similar characteristics to the human kidney, when compared with other modalities such as LF, HF, HCO, and PLM membranes.[6] The permeability characteristics of membranes are described in sieving curve. The sieving curve on the HF membrane describes a progressive decrease in sieving value which is in line with the increase in the molecular weight of the solute, until the point at which 90% of the solute is retained in the filtration process (sieving=0.1). At this molecular weight, the membrane cut-off value (molecular weight cut-off/MWCO) is determined. Conversely, the molecular weight when 10% of the solute is retained (sieving=0.9) shows the retention onset of the membrane (molecular weight retention onset/MWRO).[7]

The MWRO value can be used to differentiate membranes based on the molecular cut-off value. The MCO membrane has a cut-off value similar to that of the HF membrane. In the HF membrane, MWRO ranges in the 1200 Da (vitamin B_{12}), while MWRO for the MCO membrane ranges in the 12,000 Da (beta-2 microglobulin (b2M)). MWCO of the MCO membrane is close to the value of the HF membrane, limiting the loss of albumin.[8] For this reason, the current MCO membrane is also referred to as the HRO membrane.[6 8]

MCO MEMBRANE MOLECULAR FILTRATION TARGET

Several improvements have been made to increase the removal of medium to large uremic toxins in the dialysis process. Medium molecules are organic compounds that have a molecular weight of more than 500 Da, which can accumulate in patients with CKD and cause many complications. Middle molecule retention is associated with the development of cardiovascular disease, chronic inflammatory disease, mineral and bone disorders, secondary immunodeficiency, and amyloidosis.[9 10]

The b2M is a medium-sized molecule that is used as a marker of middle molecule removal in the dialysis process. In both pre-dialysis and dialysis patients, b2M is associated with various complications of inflammatory process, vascular stiffness, or cognitive dysfunction.[11–13] Other types of middle molecules, such as interleukin (IL)-6, are cytokines, which increase in circulating blood when kidney function decreases. Elevated IL-6 in dialysis patients is associated with cardiovascular events and left ventricular hypertrophy mortality.[14]

The MCO membrane in HDx has a tight pore size distribution, resulting in a steeper sieving curve, with MWRO and MWCO close to each other, and with a cut-off value nearly but lower than that of albumin. As a result, these membranes have the potential to remove medium to large molecular weight toxins which are increased in several conditions such as sepsis, rhabdomyolysis, and hematological disorders.[4]

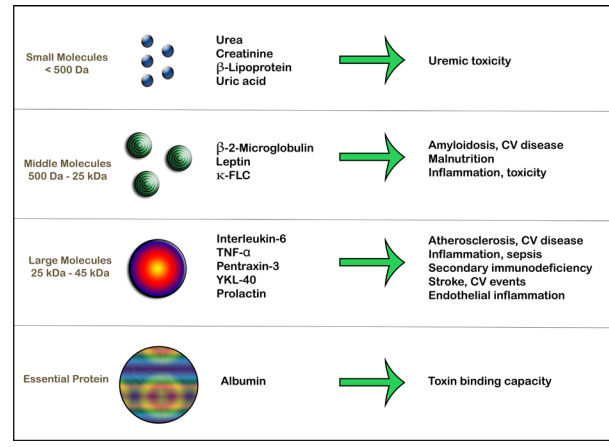

Figure 1 Various sizes of uremic toxins and their clinical manifestations. CV, cardiovascular.

Figure 1 shows various molecular sizes and their retention effects in various clinical manifestations.

THE DEVELOPMENT OF HDX

Before MCO membrane is developed, HDF is widely used in the high-flux dialysis method. Convective clearance (K) is the product of the ultrafiltration rate (Qf) and sieving (S) for a particular molecule (K=Qf×S). When the value of S is low, K must be increased by increasing Qf. This remains difficult because of limited equipment and higher cost. The development of HDF, namely online HDF, has not been widely used in many countries because it requires a complex machine with several dialysate filtration steps.[15]

The term HDx is used to describe diffusion and convection methods in a hollow-fiber dialyzer using an MCO membrane.[4] This can be done with an ordinary dialysis machine, without the need for special devices or additional instruments. In the MCO dialyzer, the inner fiber diameter is reduced from 200 µm to 180 µm, allowing for an increase in the wall shear rate and the blood rate per single fiber. This results in less residue sticking to the blood membrane and an increase in solute exchange.[16] Another additional effect is an increase in end-to-end pressure with the implication of increased cross-filtration process along the fiber.[17]

The combination of hydraulic permeability and fiber geometric structure enhances the internal filtration process.[16] The fiber bundle must have a sufficient number of fibers to cover a minimum surface area of 1.6 m^2. The number of fibers is essential to determine the cross-sectional area of the dialyzer, while the length of the fibers and dialyzers is important for optimizing internal and back-to-back filtration. This mechanism allows a large amount of convection in the dialyzer where filtration occurs in the proximal part and back filtration compensates in the distal part.[18] The ultrafiltration control system of the dialysis machine regulates the process and the proper amount of net filtration.[19] Thus, the clearance is relatively higher without the need for the fluid exchange volume normally required in HDF due to the higher sieving value of medium-large molecules.[8]

Figure 2 shows the conditions required to perform HDx. HDx does not require complex devices. Blood flow greater

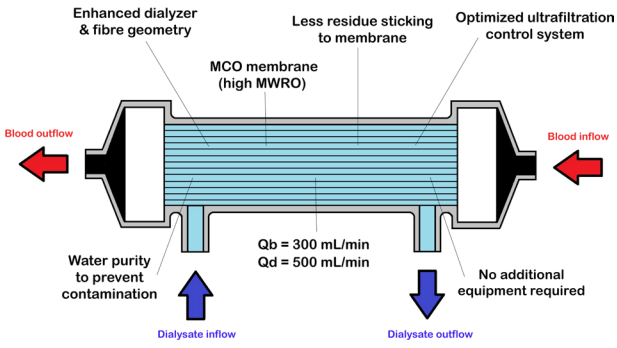

Figure 2 Essential components of HDx. HDx, expanded hemodialysis; MCO, medium cut-off; MWRO, molecular weight retention onset.

than or equal to 300 mL/min and a dialysate flow of more than or equal to 500 mL/min are sufficient to operate the machine. Water purity is also important to prevent contamination due to the large amount of back-filtration.[7] The mechanism of routine use of MCO membrane in HDx is no different from using HF-HD and does not require special technical or nursing skills related to setting, implementing, and ending dialysis.[20]

THE APPLICATION OF HDX

The goal of the dialysis process is the removal of uremic toxins that are similar to those of a human kidney, which should be able to remove molecules weighing up to 50,000 Da.[21] The evolution of a more permeable membrane such as the MCO used in HDx can provide a better clearance outcome than other membranes.

Several studies have been conducted to assess the performance of the MCO membrane in HDx. Krishnasamy *et al* conducted a cohort study called REMOVAL HD to determine the safety of using MCO dialyzers and the effect of serum albumin changes over 6 months in chronic dialysis patients. The result showed that routine use of MCO dialyzers was declared safe and did not result in a significant fall in serum albumin. There were no immediate or medium-term effects observed regarding symptoms, functional status, or nutrition on the use of the MCO membrane.[22] These results were similar to a cohort study conducted by Bunch *et al*, which described the results and trends in serum albumin levels in patients switching from conventional HF-HD to HDx. The study also reported that there were no adverse events associated with the use of MCO membrane.[23]

Zickler *et al* reported albumin levels dropped significantly after 4 weeks of MCO dialysis but increased after an additional 8-week period. In addition, HDx also increased the removal of chronic inflammatory factors over an additional 4-week and 8-week period. This indicated that HDx decreased the expression of tumor necrosis factor (TNF)-α and IL-6 genes.[24] Another study demonstrated that the use of the MCO dialyzer membrane significantly reduced the rate of infection when compared with conventional hemodialysis.[25] Moreover, a randomized controlled trial (CARTOON Study) also compared cardiovascular outcomes between patients undergoing HDx and online HDF. The result showed that HDx with MCO membrane was not inferior to online HDF in terms of cardiovascular parameters, and HDx can be an alternative where online HDF is not available in dialysis units.[26]

Other studies also examined the changes in the quality of life of dialysis patients who were assigned to HDx. By using the Kidney Disease Quality of Life-Short Form (KDQOL-SF) questionnaire, Lim *et al* examined the quality of life and characteristics of uremic pruritus of dialysis patients. The results showed that the physical functioning and physical role domain score was higher in the MCO group compared with the HF-HD group. In addition, there was also a decrease in the distribution of pruritus in the MCO group after 12 weeks of intervention.[27] Alarcon *et al* performed a cohort study called COREXH to assess the benefits of the MCO membrane which included quality of life, presence of worsening symptoms, and restless legs syndrome (RLS) diagnostic criteria. The study reported that there was a significant increase in the domains of symptoms, effects of kidney disease, and burden of kidney disease. A significant reduction was also found in the percentage of patients diagnosed with RLS after 12 months.[28]

Based on various studies, the MCO membrane with its HDx method shows the potential for better removal of toxins and chronic inflammatory factors compared with conventional HD. However, there have been some negative evaluations on certain aspects. This was reported in a study that evaluated the use of HDx in several dialysis units. Some nurses complained of difficulties in priming membranes in automatic machine mode, and some patients also required additional anticoagulants during dialysis.[29] HDx may still have limitations similar to those of HDF. Protein-bound toxin and very large uremic toxins cannot be treated with HDx, but enhancement of removal of a wide spectrum of uremic toxins via HDx is generally beneficial for dialysis patients.[30]

HDx can be an option for dialysis patients who do not achieve maximum results after conventional HD. Although several studies have shown HDx may bring promising and better benefits, larger scale studies with a longer period of time and further innovations are needed to present more significant impact on dialysis patients.

CONCLUSION

The innovation of the MCO membrane, also known as the HRO membrane, has allowed the development of a new renal replacement therapy concept called HDx. HDx is easier to perform because it does not require additional equipment or a specific dialysis nurse. By promoting the removal of more middle to large molecule toxins which conventional HD previously failed to achieve, HDx may play a key role in providing effective clearance in dialysis patients. Furthermore, future randomized control trials are warranted to reveal long-term outcomes and more potential benefits.

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ORCID iDs
Jonny Jonny http://orcid.org/0000-0002-8564-7430
Maria Teressa http://orcid.org/0000-0002-6162-6272

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