On the Balance Between Albumin Loss and Removal of Middle Molecules in Dialyzers

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BACKGROUND

Uremic toxins can be divided into small water-soluble molecules (< 0.5 kD), middle molecules (≥0.5 kD) and protein-bound solutes. Middle molecules have been classified according to weight as small-middle molecules (0.5 - 15 kDa), medium-middle molecules (> 15 - 25 kDa), and large-middle molecules (> 25 - 58 kDa). Retention of middle molecules may lead to negative outcomes, and it is believed that removing them leads to improved outcomes in patients on dialysis.

In addition to dialyzer mode, the dialyzer hollow fiber membranes play an extensive role in toxin removal. Membranes differ in mean pore radius, pore size distribution, and pure water permeability. The pore size distribution of hemodialysis membranes is essential for selectivity. Tailoring the membrane's molecular weight cut-off appropriately balances the removal of middle-molecular weight uremic toxins while avoiding albumin loss.

Low and high flux membranes are used to remove small water-soluble molecules, but do not effectively eliminate larger toxins. High cut-off membranes with larger pores than low and high flux membranes remove toxins up to 50 kDa, but due to their large pore size distribution also allow unwanted albumin loss, which could lead to hypoalbuminemia. Medium cut-off membranes are designed to remove middle molecules up to 50 kDa, but due to their sharper pore size distribution, they can offer lower albumin loss.

Use of medium cut-off membranes with hemodialysis or expanded hemodialysis therapy has been investigated in numerous clinical studies with the overall consensus that expanded hemodialysis therapy improves the clearance of a wide range of middle molecules, and can improve quality of life, morbidity, and mortality. Various medium cut-off membranes are available from different manufacturers with potentially different properties.

OBJECTIVE

The current study aims to determine the plasma clearance of middle molecules (12 - 52 kDa) and the albumin loss in four commercially available dialyzers:

- **Theranova** 500 dialyzer (Gambro Dialysatoren GmbH)
- Phylther HF20SD from Bellco Mirandola
- VitE 21 X (Asahi Kasei Medical Co., Ltd)
- Elisio 19 HX (Nipro Medical Corp.)

Five dialyzers from each type were tested.

METHODS

This study was a comprehensive ex-vivo investigation of performance characteristics of four different commercial dialyzers. Membrane pore characteristics were analyzed, ex-vivo experiments were performed to evaluate the clearances of significant middle molecules, and experiments at different blood flow rates quantified the influence on middle molecule clearance and albumin loss.

Dextran sieving experiments

Dextran sieving experiments were done to characterize the membranes. From the resulting sieving curves, the retention and the pore size distribution can be derived. In order to provide a comparable result, measurements were performed according to Boschetti-de Fierro et al. (2013)[1] using different dextran fractions. Dextran concentrations were measured with an Agilent HPLC 1200 equipped with a TSK gel column from Tosoh Bioscience. The pore size distribution was then calculated from the sieving curves.

Plasma clearance

Anti-coagulated (citrate) human plasma Octaplas from Octapharma with a protein concentration of 55 ± 10 g/L was used, and the following extrinsic marker substances were spiked in the plasma to measure clearance: 5 mg/L of LEE Biosolutions' ß2 microglobulin (ß2m) (M_w = 12 kDa) and Myoglobin (Myo) (M_w = 17 kDa). YKL-40 (MW = 40 kDa) is an intrinsic marker, therefore the initial concentration might vary for different plasma charges. The plasma volume loss due to ultrafiltration was compensated by substituting dialysate into the plasma pool, and the temperature was set to 37 °C to mimic the human body. Set-up is shown in Figure 1.

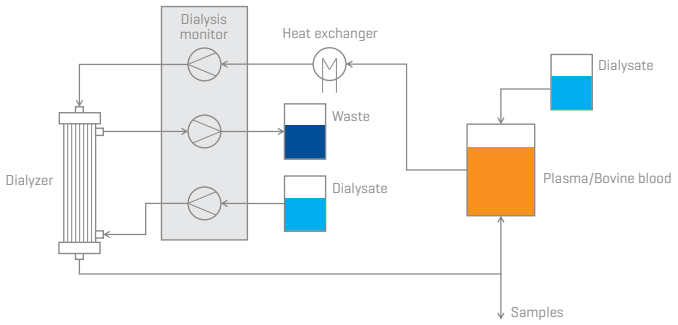

FIGURE 1. Experimental setup for the plasma clearance and albumin loss measurements.