EXPANDED HEMODIALYSIS *VERSUS* ONLINE HEMODIAFILTRATION: A PILOT STUDY ON INTRADIALYTIC HEMODYNAMICS AND FLUID STATUS

Paola da Ponte Silva, Hugo Abensur, Rosilene Motta Elias, Benedito Jorge Pereira, Cláudio Luders, Marcelo Augusto Duarte Silveira, Isis de Sousa Ferreira Cordeiro, Bruno Caldin da Silva

Institution

Department of Medicine, Renal Division, University of São Paulo, São Paulo, Brazil

NCT ID not yet assigned

Unique Protocol ID: 16928

Document Date: 09/06/2017

Corresponding author:
Bruno Caldin da Silva, M.D., Ph.D
Renal Division, University of São Paulo.
Rua Dr. Enéas de Carvalho Aguiar 255, 7th floor,
São Paulo, SP, Brazil,
Postal Code: 05403-000, São Paulo, SP, Brazil
Phone: +55-11-99762-0521; Fax: +55-11-30967683
E-mail: brunocaldin@hotmail.com

Abstract

Conventional hemodialysis (HD) is essential for the treatment of end-stage renal disease (ESRD) patients, by reducing serum concentration of uremic toxins and correcting fluid overload.

Nevertheless, HD removes almost exclusively low-range uremic toxins. Therefore, medium-range molecules, such as beta-2-microglobulin might accumulate in tissues, leading to many clinical complications, such as neuropathies, tendinopathies, anemia, bone mineral disease and reduced growth in children.

Convective methods might reduce incidence of these complications, by removing molecules of medium-range molecular weight. Online hemodiafiltration (olHDF) is the most extensively used method in this regard. Nevertheless, there are some barriers to the wider introduction of this method in clinical practice, since specific machines are needed for this procedure, the costs with dialysis lines are higher and water consumption increases. More recently, the development of new membranes for hemodialysis allowed removal of medium- and high-range uremic toxins, with albumin retention. Thus, they allow removal of a broad range of uremic toxins, without changing dialysis machine or increasing water comsumption. Such therapy is known as expanded hemodialysis (HDx).

The aim of this present study is to compare the extraction of middle-size molecules, the hemodynamic behavior, fluid and nutritional status of patients submitted to olHDF or HDx, in a crossover study.

Introduction

End-stage renal disease (ESRD) is a condition characterized by marked decline in renal function, usually at rates below 10 ml/min/1.73 m². In Brazil, there are about 110,000 patients on maintenance hemodialysis (HD) and mortality rates are around 19%.(1)

The explanation for this high mortality rate derives from comorbidities such as Diabetes Mellitus, arterial hypertension and left ventricular hypertrophy.(2-4) Additionally, these patients are submitted to extracorporeal circulation, with intense body fluid variation and electrolyte composition during procedure. Besides, several uremic toxins are not removed during HD sessions.(5)

Improvement of dialysis and membrane technologies has flourished in the last decades. They have provided better management of these patients and prolonged survival.

Uremic syndrome

Uremic syndrome is characterized by several clinical manifestations resulting from the progressive loss of renal function, with biochemical, fluid and functional alterations.(6, 7)

Uremic toxins have different molecular weights. The most frequently reported is urea, which has molecular weight of 60 Da and is used as a marker of HD quality. Low molecular weight solutes are readily dialyzable by conventional HD. Intermediate molecular weight (IMW) solutes have a molecular weight between 500 and 60000 Da. Among them are beta-2-microglobulin (β2M), which is associated with dialysis-related amyloidosis, leptin, related to malnutrition, prolactin, which is associated to infertility of women in dialysis, hepcidin, related to the anemia of patients with CKD, among others.(8, 9) IMW solutes are not significantly removed by conventional HD and tend to accumulate in the organism of dialytic patients.(10) More recently, membranes for HD with high permeability to medium molecules and with selective retention of albumin have also emerged as an option to convective therapies. Such modality is known as expanded hemodialysis (HDx).(11)

Online Hemodiafiltration

The olHDF technique combines diffusion with high convection rates in which the dialysis fluid, free of toxins and pyrogens, is used to prepare the replacement fluid.(12)

The online module of dialysis machine prepares the replacement fluid by a cold sterilization process. There is a cross-flow water preparation, in order to avoid the accumulation of possible contaminants. The addition of bicarbonate and acid solutions to water follows the process. Next, the ready-for-infusion dialysis solution is passed through another ultrafilter prior to being infused into patients. The microbiological safety of these systems is demonstrated in clinical studies with an absence of activity-inducing cytokines and pyrogenic reactions.(13, 14)

Some studies have compared olHDF with HD. The Contrast study(15) included 714 patients, with an average follow-up of 3 years. There were no differences in mortality in both modalities. However, for replacement volume above 21.95L, there was reduction in mortality of olHDFol group. The Turkish study(16) also presented similar data, without differences in general mortality, with the exception of the subgroup of patients with a replacement volume greater than 17.4L.

The Eshol study,(17) which included 906 patients, with an average follow-up of 1.91 years, showed a reduction in mortality using olHDF, regardless of the replacement volume used. In this study, mean replacement volume was 23.7L.

Dialysis membranes

Blood-dialysate interaction through semi-permeable membranes has always characterized dialysis methods since the first dialysis sessions in the mid-twentieth century.

Some physical characteristics determine the dialysis membranes:

- KoA: determines the permissibility to the diffusion of small molecules, in the presence of ideal diffusion conditions (with theoretically infinite blood and dialysate flows);

- Kuf: is determined by hydraulic conductance of a membrane in the presence of a transmembrane pressure;

- sieving: proportion of molecules that can cross the membrane, according to their molecular weight.

The diffusive process depends fundamentally on the density of pores in the membrane. The ultrafiltration and sieving properties vary depending on the mean pore diameter of the membrane.

The size of the pores determines which molecules are allowed to move across membranes. The molecular size at which the sieving coefficient is only 0.1 is termed membrane's cutoff value. That is, molecules with molecular weight above this value are unlikely to cross the membrane.

However, the cutoff value is not the only one that defines the permeability of a membrane. Another parameter, termed "retention onset" (RO) should also be determined for this purpose. It describes the molecular weight/radius where the sieving value is 0.9. Besides, dialysis membranes can have different pore sizes. Membranes with a more heterogeneous distribution of pore size may present greater loss of albumin than a membrane with more homogeneous sizes of these pores, although both have the same cutoff values.(11)

High cutoff membranes have recently been introduced into clinical practice, with the potential benefit of removing toxins with high molecular weight, typically associated with sepsis, rhabdomyolysis and hematological diseases, such as inflammatory cytokines, myoglobin, free light chains. Such membranes, however, also lead to loss of albumin, which can lead to or aggravate malnutrition.

More recently, membranes with high cutoff values, but with tight pore size distribution have been developed. The main concept is to keep both cutoff and retention onset values close to each other, but with a cutoff value lower than of albumin. This should allow removal of middle-to-high weight range uremic toxins, with very low albumin leak. Thus, these membranes, denominated high retention onset (HRO) membranes, allow performing both diffusive and convective processes in a conventional hemodialysis machine. These new HRO membranes defined a new modality of HD, denominated expanded hemodialysis (HDx).

Hypothesis

Our hypothesis is that HDx is noninferior to olHDF in the following parameters:

- Hemodynamic stability
- Nutritional and fluid status
- Removal of beta-2 microglobulin

Objectives

To evaluate each patient, through a prospective, randomized and cross-over study, the intradialytic hemodynamic behavior, fluid and nutritional status assessed by electrical bioimpedance and B2M removal in two dialytic modalities: HDFol versus HDx.

Subject and Methods

Inclusion criteria

Adult patients who are on maintenance HD at Hospital das Clínicas and agree to participate in the study by signing the informed consent form.

Exclusion criteria

Patients who cannot understand or who refuse to sign the informed consent form;
Patients who are currently on daily HD or olHDF.

Concise methods

a) Clinical and laboratorial data

Clinical data will be collected from the institution's chart, recorded and filled with all necessary precautions to keep confidentiality of patient's information. They are: baseline renal disease, age, history of smoking, sedentary lifestyle, presence of comorbidities such as hypertension and diabetes mellitus, family history of cardiovascular disease, history of coronary and cerebrovascular disease and medications.

Laboratory tests used to determine the biochemical, hematological and bone mineral profile characteristics will be obtained from routinely collected

exams. Such exams are processed by the Central Laboratory of Hospital das Clínicas / FMUSP.

b) Dialysis

All dialysis procedures will be performed by the Dialog+ Admea™ machine (BBraun Melsungen AG, Germany).

The olHDF will be prescribed as follows: blood flow 350 - 400 ml/min, dialysate flow 800 ml/min, post-dilution flow (90-100 ml/min), with high-flux Xevonta™ (BBraun Melsungen AG, Germany) or CAHP/DICE™ (Baxter Healthcare Corporation, Deutschland) dialyzers, with surface area of 1.7-2.4 m^2. The duration of each session will be from 3,5h to 4h, depending on current dialysis prescription. Total substitution volume will be higher than 20 L per session.

HDx will follow the same prescription of olHDF, regarding blood and dialysate flows and dialysis duration. There will be no substitution volume. Theranova™ dialyzers (Baxter Healthcare Corporation, Deutschland) will be used for each session.

Before initiating protocol and during the washout period, patients will be submitted to high-flux HD, which is the standard treatment in our service.

c) Hemodynamic monitoring

Cardiac output index (CI), stroke volume (SV - integrated mean of the flow waveform between the current upstroke and the dichotic notch), peripheral arterial resistance (PAR - ratio of mean arterial pressure to stroke volume multiplied by heart rate) and blood pressure (BP) will be accessed by finger beat to-beat monitor Finometer™ (Finapress Medical Systems BV, Arnhem, The Netherlands), within 15 minutes after starting olHDF or HDx sessions (predialysis) and again, 15 minutes before its end (post-dialysis), according to a previous studies of our group.(18-20).

d) Biolectrical impedance

Segmental tetrapolar bioelectrical impedance (BIS) will be performed in all patients while recumbent, before starting study protocol and before each phase of the study (HDx or olHDF), by the multifrequency InBody™ S10

(Biospace Co., Ltd., Korea) device. It allows assessment of the following parameters regarding body fluids: total body water, total extracellular body water, lower limbs total water content, lower limbs extracellular water content. Additionally, α-angle, which is a marker of cellular integrity and nutritional status, will be noted.(21)

e) Blood and Effluent samples

Blood samples will be collected pre-session, mid-session and post-dialysis sessions, both in the first and last dialysis sessions of each of the periods studied (HDFol or HDx). Pre-session blood samples will be collected immediately after arteriovenous fistula puncture and the middle and post-session samples will be collected from the arterial line, 2 minutes after reduction of blood flow to 50 ml/min and suspension of dialysate flow and/or replacement.

In addition, partial and homogeneous collection of the effluent will be performed by a drainage hose, with an infusion pump operating continuously at a rate of 1l/h, as previously validated in the literature,(22-25) and successfully replicated by our service.(26, 27) The whole effluent of dialysis session will be collected.

Description of study design and procedures are described in figure 1. Blood and effluent samples to be collected are depicted in table 1.

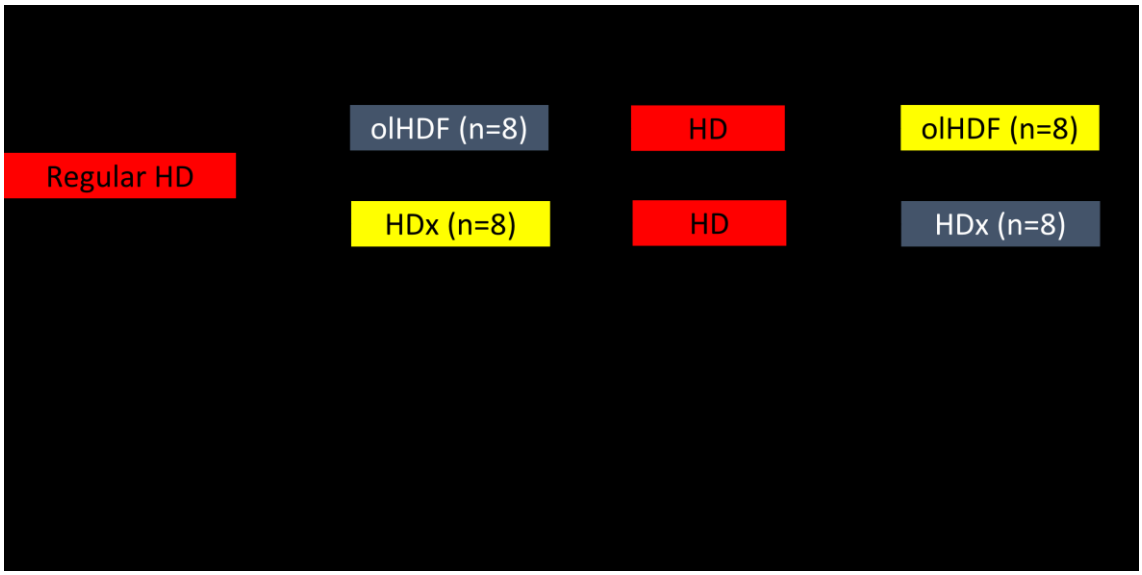

Figure 1. Protocol description

Table 1. Description of Serum and effluent samples

Blood	**First Sample (pre-dialysis)**	**Second Sample (mid-dialysis)**	**Third Sample (post-dialysis)**
Albumin	X	X	X
β2-microglobulin	X	X	X
Creatinin	X		X
Phosphorus	X	X	X
Hematocrit	X		
Hemoglobin	X		
Total Protein	X	X	X
Urea	X	X	X
Effluent			
Albumin		X	
β2-microglobulin		X	
Phosphorus		X	
Urea		X	

Statistical Analysis

According to parametric distribution or not of the studied variables, paired t test or Wilcoxon's test will be used, respectively. The following variables will be compared in the two following situations HDFol *versus* HDx, HDFol *versus* high-flux HD and HDx *versus* high-flux HD:

- Pre-dialysis serum samples: albumin, β2-microglobulin, creatinine, phosphorus, hematocrit, hemoglobin, total proteins, urea;
- Intradialytic serum samples: albumin, β2-microglobulin, phosphorus, total proteins, urea;
- Post-dialysis serum samples: albumin, β2-microglobulin, creatinine, phosphorus, total proteins, urea;
- Intradialytic effluent samples: albumin, β2-microglobulin, phosphorus, total proteins, urea;
- Pre-dialysis hemodynamic variables: blood pressure, cardiac index;
- Post-dialysis hemodynamic variables: blood pressure, cardiac index, systolic volume, peripheral vascular resistance;
- Pre-dialysis bioimpedance variables: extracellular water / total body water ratio and α-angle;
- Post-dialysis bioimpedance variables: extracellular water / total body water ratio and α-angle.

Next steps

1 Recruitment of sixteen patients from the hemodialysis service of Hospital das Clínicas, University of São Paulo;

2 Submission to local ethics Committee: Comissão de Ética para Análise de Projetos de Pesquisa (CAPPesq). Protocol number: 16928/2017. Date of submission: 07/31/2017;

3 Submission to Baxter Healthcare Corporation: 07/31/2017;

4 Upon approval by both CAPPesq and Baxter Healthcare Corporation, study protocol will be registered in "Clinical Trials" platform;

5 Study will start immedialtely after completion of item 4. The estimated time to complete the study is four months;

6 After data compilation and analysis, a manuscript will summarize this study for further publication.

References

1. Sesso RC, Lopes AA, Thome FS, Lugon JR, Martins CT. Brazilian Chronic Dialysis Census 2014. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2016;38(1):54-61. Epub 2016/04/07.

2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. Journal of the American Society of Nephrology : JASN. 2004;15(8):2208-18. Epub 2004/07/31.

3. Manjunath G, Levey AS, Sarnak MJ. How can the cardiac death rate be reduced in dialysis patients? Seminars in dialysis. 2002;15(1):18-20. Epub 2002/03/05.

4. Spiegel DM, Raggi P, Smits G, Block GA. Factors associated with mortality in patients new to haemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2007;22(12):3568-72. Epub 2007/07/10.

5. Vanholder R, De Smet R. Pathophysiologic effects of uremic retention solutes. Journal of the American Society of Nephrology : JASN. 1999;10(8):1815-23. Epub 1999/08/14.

6. Boure T, Vanholder R. Biochemical and clinical evidence for uremic toxicity. Artificial organs. 2004;28(3):248-53. Epub 2004/03/30.

7. Goodkin DA, Mapes DL, Held PJ. The dialysis outcomes and practice patterns study (DOPPS): how can we improve the care of hemodialysis patients? Seminars in dialysis. 2001;14(3):157-9. Epub 2001/06/26.

8. Feinfeld DA, Rosenberg JW, Winchester JF. Three controversial issues in extracorporeal toxin removal. Seminars in dialysis. 2006;19(5):358-62. Epub 2006/09/15.

9. Winchester JF, Audia PF. Extracorporeal strategies for the removal of middle molecules. Seminars in dialysis. 2006;19(2):110-4. Epub 2006/03/23.

10. Maduell F, Navarro V, Torregrosa E, Rius A, Dicenta F, Cruz MC, et al. Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. Kidney international. 2003;64(1):305-13. Epub 2003/06/06.

11. Ronco C. The Rise of Expanded Hemodialysis. Blood purification. 2017;44(2):I-VIII. Epub 2017/05/10.

12. Ronco C, Brendolan A, Everard P, Irone M, Ballestri M, Cappelli G, et al. Cellulose triacetate: another membrane for continuous renal replacement therapy. Journal of nephrology. 1999;12(4):241-7. Epub 1999/09/24.

13. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, et al. Effect of membrane permeability on survival of hemodialysis patients. Journal of the American Society of Nephrology : JASN. 2009;20(3):645-54. Epub 2008/12/19.

14. Maggiore Q, Pizzarelli F, Dattolo P, Maggiore U, Cerrai T. Cardiovascular stability during haemodialysis, haemofiltration and haemodiafiltration. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2000;15 Suppl 1:68-73. Epub 2000/03/29.

15. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. Journal of the American Society of Nephrology : JASN. 2012;23(6):1087-96. Epub 2012/04/28.

16. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2013;28(1):192-202. Epub 2012/12/12.

17. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. Journal of the American Society of Nephrology : JASN. 2013;24(3):487-97. Epub 2013/02/16.

18. Silva BC, Freitas GR, Silva VB, Abensur H, Luders C, Pereira BJ, et al. Hemodynamic behavior during hemodialysis: effects of dialysate concentrations of bicarbonate and potassium. Kidney & blood pressure research. 2014;39(5):490-6. Epub 2014/12/23.

19. Silva BC, Moyses RM, Silva VB, Freitas GR, Elias RM. Parathyroidectomized patients have impaired capacity of peripheral vascular constriction during hemodialysis. Hemodialysis international International Symposium on Home Hemodialysis. 2016;20(1):50-5. Epub 2015/04/30.

20. Jimenez ZN, Silva BC, Reis LD, Castro MC, Ramos CD, Costa-Hong V, et al. High Dialysate Calcium Concentration May Cause More Sympathetic Stimulus During Hemodialysis. Kidney & blood pressure research. 2016;41(6):978-85. Epub 2016/12/16.

21. Oliveira CM, Kubrusly M, Mota RS, Silva CA, Choukroun G, Oliveira VN. The phase angle and mass body cell as markers of nutritional status in hemodialysis patients. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2010;20(5):314-20. Epub 2010/03/23.

22. Argiles A, Ficheux A, Thomas M, Bosc JY, Kerr PG, Lorho R, et al. Precise quantification of dialysis using continuous sampling of spent dialysate and total dialysate volume measurement. Kidney international. 1997;52(2):530-7. Epub 1997/08/01.

23. Charytan C, Gupta B, Meindel N, Spinowitz B. Fractional direct dialysis quantification: a new approach for prescription and monitoring hemodialysis therapy. Kidney international. 1996;50(6):1845-9. Epub 1996/12/01.

24. Cheng YL, Shek CC, Wong AK, Wong FK, Chau KF, Li CS. A partial dialysate collection method. The International journal of artificial organs. 1997;20(1):14-7. Epub 1997/01/01.

25. Cheng YL, Shek CC, Wong FK, Choi KS, Chau KF, Ing TS, et al. Determination of the solute removal index for urea by using a partial spent dialysate collection method. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1998;31(6):986-90. Epub 1998/06/19.

26. Karohl C, de Paiva Paschoal J, de Castro MC, Elias RM, Abensur H, Romao JE, Jr., et al. Effects of bone remodelling on calcium mass transfer during haemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(4):1244-51. Epub 2010/02/02.

27. Alvares VRC, Ramos CD, Pereira BJ, Pinto AL, Moyses RMA, Gualano B, et al. Pneumatic Compression, But Not Exercise, Can Avoid Intradialytic Hypotension: A Randomized Trial. American journal of nephrology. 2017;45(5):409-16. Epub 2017/04/14.