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Fifteen Years of Experience with On-Line Hemodiafiltration

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Abstract

Hemodiafiltration (HDF) with elevated substitution fluid offers an optimal way of removing uremic substances. The beginnings of HDF and on-line HDF, learning curve, differences in the removal of uremic toxins, difficulties in the development, automated manual Q_i as a practical way of prescribing, distinct experiences with on-line HDF and prospective, randomized ongoing on-line HDF studies are detailed as a personal vision for 15 years' handling with on-line HDF.

Hemodialysis ensures the survival of close to 2 million patients with chronic renal failure worldwide. After more than four decades of chronic dialysis treatment, the level of technological development is satisfactory and hemodialysis can be considered a routine renal replacement therapy with guaranteed short-term safety. The long-term clinical outcome, however, could be improved. Malnutrition is common, hyperphosphatemia, hypertension and heart failure control is poor, rehabilitation and quality of life are suboptimal, and hospitalization and mortality rates are high. Cardiovascular disease is the most common cause of mortality in chronic hemodialysis patients and is the reported cause of death in approximately 50%. Depner defined this situation as a residual syndrome that includes susceptibility to infection, reduced maximal oxygen consumption during exercise, sleep disturbances, depression, impaired mental concentration, reduced stamina and markedly increased susceptibility to cardiovascular complications.

Beginnings of Hemodiafiltration

In the 1990s, there were several priorities in the field of hemodialysis. The first aim was to reduce dialysis time to 3.0–3.5 h per session in order to improve patient quality of life. This required increased solute removal during the session using increases in blood flow (Q_b), dialysate flow (Q_d) and dialyzers with a larger surface area (1.6–2.1 m^2). Technological advances in dialysis machines, especially volumetric control of ultrafiltration and the widespread use of bicarbonate in the dialysis fluid, allowed the use and development of synthetic dialyzers with larger pores and high hydraulic permeability. Thus, blood depuration of higher molecular weight substances could be achieved. These membranes heralded a new era in hemodialysis and opened new fields of study and treatment, namely high-flux hemodialysis and convective techniques such as hemofiltration and hemodiafiltration (HDF). Initially, given the design of dialysis machines, simple HDF techniques were used that involved off-line production of replacement fluid. The initial experience gained with HDF techniques was used in Spain to shorten the length of the dialysis sessions. HDF increased efficacy and tolerance of treatment, and the high quality of the dialysis fluid/substitution fluid used avoided the type of back-filtration-induced adverse reactions reported when high-flux membranes were first introduced. Exogenous replacement fluid was necessary but was limited to <10 liters per session for practical reasons (infusion replacement was limited by the dialysis machine to 2 l/h; 4 l/h when a precision balance was used) and financial considerations (exogenous solutions are expensive). These HDF techniques included biofiltration, conventional HDF, paired filtration dialysis and acetate-free biofiltration. High-flux hemodialysis is a form of low-volume HDF because of the internal filtration and back-filtration that can take place within a dialyzer. Although quantification of back-filtration is still controversial, flow rates were estimated by Dr. Claudio Ronco et al. to be up to 30 ml/min, and may generate 4–8 liters of back-filtration in a 4-hour session. Clinical experience has confirmed that there are no differences between high-flux dialysis and low-volume HDF.

During the 1990s, nephrologists were aware that water treatment was adequate but still did not meet the requirements for water for ultrapure dialysis fluid. Consequently, the entry of dialysis fluid into the blood compartment (called back-filtration) was avoided as much as possible. Acute symptoms were listed as pyrogenic reactions, hypoxia and hypotension, while chronic symptoms were understood to be chronic inflammation, increased susceptibility to infections, amyloidosis, malnutrition and arteriosclerosis.

Beginnings of On-Line Hemodiafiltration

To perform HDF with large volumes of replacement fluid, a feasible technique for preparing cheap, clean substitution fluid is required. Many approaches have

been employed to test and ensure the microbiological quality of the water used for dialysis or dialysate. These technical innovations have enabled on-line production of ultrapure substitution fluids in large quantities for high-efficiency HDF procedures. After Henderson successfully produced sterile, pyrogen-free solutions by ultrafiltration in 1978, several new HDF techniques appeared with large-volume, on-line preparation of replacement fluid for HDF. These new HDF techniques included high-flux HDF and on-line HDF.

High-Flux HDF. Von Albertini achieved very high clearances for both small and large solutes using two large high-flux dialyzers in series and adjusting the pressures over the filters so that ultrafiltration occurs only in the first filter and back-filtration only in the second filter. Ultrafiltration in the first device was 116 ml/min and the total filtrate removed per 2-hour treatment session averaged 13 liters. One member of this research group, Dr. Juan Bosch, was invited to a symposium on 'Advances in Hemodialysis' in Burgos, Spain, in 2004, to speak about this experience. His presentation taught me personally that, if pure water and ultrapure dialysate are available, back-filtration can become an effective ally in achieving better solute removal.

Dialysis machines have been modified to perform on-line HDF. This technique involves adding one or two filters at intermediate points in the dialysate line to produce clean dialysate, and an infusion pump to divert a specific fraction of the dialysate produced (50–200 ml/min or 3–12 l/h). The total infusion volume is limited only by the blood flow (one-third of blood flow) and the transmembrane pressure (TMP), which is determined by the ultrafiltration, hematocrit, total proteins and session length. With blood flow rates of 350–450 ml/min and infusion rates of 100–130 ml/min, over 24–32 liters of convective transport is provided during a 4-hour treatment session. Dr. Bernard Canaud showed that on-line HDF is a safe, well-tolerated technique and good clinical results have been observed with the first prototype dialysis machines in Europe.

In Spain, the first experiences date back to 1993, in Granada, where Dr. Juan Garcia-Valdecasas, who had previously visited von Albertini's group, was interested in highly convective techniques and reinfusion dialysis fluid and had the opportunity to work with on-line HDF prototype machines with satisfactory results. I was very interested in these techniques and followed these initial experiences with great interest. Then, in September 1996, I had the opportunity to work with the first machines marketed for on-line HDF.

Working with high-volume HDF techniques was highly gratifying because they offer several advantages over conventional low-flux or high-flux hemodialysis methods, as well as over low-volume HDF techniques. First, the use of high-permeability synthetic membranes, which provide the best biocompatibility, is required. Second, HDF with high volumes of replacement fluid is an optimal way of removing uremic substances over a wide range of molecular sizes, from small solutes to low-molecular-weight proteins. Third, performance of these

techniques requires the use of ultrapure dialysate, which provides other benefits for the patient [1–9].

Patients' opinions and their degree of satisfaction with clinical and laboratory findings quickly confirmed that we were on the right road. Furthermore, as in most groups, we discontinued short dialysis and switched to three times weekly sessions of a minimum of 4 h each.

Learning Curve in On-Line Hemodiafiltration

Blood Flow

In on-line HDF, the most important limiting factor for the infusion rate (Q_i) is the blood flow (Q_b) and TMP [10]. Machines for post-dilution HDF allow an infusion rate of 30% of Q_b, so this is the approach we took in the beginning. Later, with the experience gained, we concluded that a Q_i of 25% or less of Q_b is preferable in order to avoid increasing the blood viscosity and causing clotting complications within the circuit. These complications trigger numerous machine alarms that affect the normal operation of a treatment session for both the patient and the medical staff. To optimize the use of post-dilutional HDF, we recommend a Q_b of between 360 and 500 ml/min with a Q_i of between 80 and 125 ml/min.

Dialyzers

We were also curious to examine whether the choice of dialyzer for on-line HDF is important [11]. In a study of eleven different dialyzers, only triacetate and PMMA (polymethylmethacrylate) were found to be of limited use for conducting on-line HDF, basically because of TMP-related problems. The other dialyzers evaluated (i.e. polysulfone and derivatives, polyamide, polyacrylonitrile, AN69 and PEPA) could perform on-line HDF without problems at similar TMPs controlled by the dialysis machines.

Vascular Access

Initially an arteriovenous fistula was considered the best and only option for on-line HDF. However, the use of catheters has increased in recent years (between 15 and 20% of patients on hemodialysis). Because of the aging population and increased prevalence of vascular disease, tunneled catheters were reconsidered in on-line HDF patients. In 1998, Canaud et al. published 7 cases of permanent catheters in on-line HDF and Maduell et al. reported 8 cases of on-line HDF in patients with tunneled catheters and a Q_b of 372 ml/min with a mean infusion volume of 20.1 ± 4 liters (between 18 and 25 liters).

Pre-Dilutional, Post-Dilutional or Mixed Infusion

After a review of the literature and our own studies, we believe that post-dilutional infusion is the most effective form of infusion for the removal of all

substances (small, medium and large molecules) – even if part of the circuit may be susceptible to technical problems because of hemoconcentration and increased TMP. Pre-dilutional infusion prevents some such technical problems but reduces the clearance of solutes due to dilution of their concentrations. Mid-dilution is a recent alternative with infusion taking place in the middle of the dialyzer, whereby infusion is post-dilution HDF for the first half of the dialyzer and pre-dilution HDF for the second half. This provides similar or even superior results to the post-dilution mode [12, 13]. We still await the practical application and results of mixed dilution HDF, which is characterized by simultaneous pre- and post-dilution and autoregulation of both flows. This could optimize efficacy and avoid hemoconcentration.

Differences between Hemodialysis and On-Line Hemodiafiltration Regarding Removal of Uremic Toxins

Solute removal is the primary goal of dialysis and, as 50,000 Da is the cut-off of the natural kidney, substances up to this molecular weight should ideally be removed. Different solute clearance profiles are obtained depending on the treatment mode selected. HDF with high volumes of replacement fluid seems to be the most effective technique for removing all small, medium-sized and large molecules. Low-flux hemodialysis only removes solutes with molecular weights of less than 5,000 Da. Several studies have analyzed the removal capacity of different treatment modes over a broad spectrum of solutes. Urea and creatinine clearances largely depend on diffusion processes. Small solutes (<500 Da) are effectively removed by all treatment modes except hemofiltration. β_2-Microglobulin (11,800 Da) is not removed by low-flux hemodialysis because this molecule is larger than the membrane pore size. Thus its clearance is largely achieved by high-flux dialysis and convection processes. Kerr et al., Lornoy et al. and Maduell et al. have reported a reduction rate for β_2-microglobulin of 50–60% in high-flux hemodialysis and of 70–80% in on-line HDF.

Our group was also very interested in the removal of solutes of molecular weight exceeding that of β_2-microglobulin [14–16]. The use of high-volume convection techniques plays an important role in the removal of solutes larger than 15,000 Da during hemodialysis. Like β_2-microglobulin, however, these larger molecules have a low distribution volume and/or follow a multicompartmental model as reflected by the difficulties of normalizing predialysis plasma concentrations. Healthy kidneys work 24 h a day to maintain normal levels of uremic toxins. The results of our studies suggest that the removal of solutes larger than β_2-microglobulin, such as myoglobin, prolactin and α_1-microglobulin, is difficult with high-flux therapies so that highly convective treatment could possibly be applied. Other studies support this hypothesis: Lepenies et al. observed that the extraction ratio for leptin was higher with convective techniques, and Ward

et al. studied complement factor D and found that its removal was significantly higher for on-line HDF than for high-flux hemodialysis.

Difficulties in the Development of On-Line Hemodiafiltration

The expansion of convective techniques to becoming routine treatment has been delayed for technological and economic reasons. Hemofiltration or HDF modalities require the use of high-permeability dialyzers and, at the same time, machines with volume control and a dual pump. Replacement fluid constitutes a further cost factor: this was the main reason for abandoning hemofiltration (replacement volumes exceed 20 liters), and was a key constraint in the initial HDF technique with volumes ranging between 3 and 10 liters. Finally, the introduction of on-line HDF techniques using the dialysis fluid itself as a replacement solution has required major changes to be made to hemodialysis units. It has taken another 10 years to refurbish and upgrade water treatment systems, acquire specific machines and incorporate safety filters to ensure a high quality of this replacement fluid (ultrapure dialysate).

The availability of excellent water treatment systems and ultrapure dialysate has led to a breakthrough in the clinical treatment of patients on dialysis and represents the first major achievement of on-line HDF. Nevertheless, on-line HDF was only used in less than 10% of patients in 2000. Another essential requirement for routine use of on-line HDF is tests for endotoxin determination, which often had to be referred to outside laboratories.

'Automated Manual Q_i' Is a Practical Way of Prescribing Post-Dilution On-Line Hemodiafiltration

The most commonly used mode of infusion is post-dilution on-line HDF, since it provides high clearance of small and large solutes although it can cause a greater number of complications related to hemoconcentration and TMP. While the pre-dilution mode partially solves such technical problems, it also reduces the efficiency of solute removal because of hemodilution. Hemodialysis research is currently aimed at obtaining safer, more practical and effective systems, which largely depend on technical advances to improve dialysis machines. Specifically, to adjust the replacement rate of a manual post-dilution on-line HDF treatment, the recommended Q_i is 25% of Q_b. Some of these machines (Fresenius 5008) offer the possibility to automatically adjust Q_i with a formula using real values for total protein and hematocrit. Furthermore, the ultrafiltration coefficient is measured in the first few minutes of the dialysis session and subsequently every hour. Additional measurements are performed if any unexpected events occur. The cyclic pressure test is performed, which estimates and monitors (by

means of TMP) the behavior of the dialyzer curve during treatment, progressively adjusting Q_i.

If we decide to graduate Q_i manually, the machine will not modify Q_i automatically and we have to modify this value when we detect an alarm or warning on the machine resulting from TMP increases. Indeed automatic Q_i modification may not even be feasible if hematocrit and total protein values are not known (one does not always have the results of analysis for each session), as these are required for the formula. In such a case, one can use 'automated manual' or 'alarm-free' treatment. Here we prescribe a Q_i value automatically by adjusting hematocrit and total protein values to obtain a Q_i value for manual prescription at the beginning of the session.

In a study performed in 2007, our group showed that automated manual Q_i prescription in post-dilution on-line HDF is able to meet the treatment prescription (normally a Q_i of about 25% of the Q_b) with an individual intradialysis adaptation according to blood viscosity and hemoconcentration [17]. We concluded that prescription of automated manual Q_i is a practical way of prescribing post-dilution on-line HDF in which maximum efficacy and total replacement volume are achieved with a significant reduction in the number of alarms during dialysis. This, consequently, improves the patients' clinical course without delaying the end-time.

Distinct Experiences with On-Line Hemodiafiltration

Daily On-Line HDF

In September 2001, our group decided to combine the most physiological and effective dialysis schedule (daily dialysis) with on-line HDF [18, 19]. Patients on standard 4- to 5-hour three times weekly on-line HDF were switched to 2- to 2.5-hour six times weekly on-line HDF. Although the dialysis time was similar in both treatment schedules, an increase in the dialysis dose was obtained with the daily scheme, confirming the beneficial effect of the higher frequency. The principal advantages observed in this study were excellent clinical tolerance and patient acceptance, disappearance of post-dialysis fatigue, improvement of sleep disorders, higher removal of middle and large molecules with a 21% reduction in predialysis plasma β_2-microglobulin levels, a reduction in phosphate binders, improvement of nutritional status (body weight increased from 67.8 ± 8 to 69.4 ± 8 kg after 6 months and to 70.9 ± 9 kg after 1 year), better control of blood pressure without antihypertensive medication and regression of left ventricular hypertrophy.

Nocturnal, In-Center, Every-Other-Day On-Line HDF

In 2007, we began a new phase in Hospital Clinic in Barcelona when we sought to combine the most physiological and effective dialysis schedule,

long (nocturnal) and more frequent (every-other-day) dialysis with the dialysis modality that offers the highest solute and uremic toxin removal (on-line HDF). The aim of this study was to switch patients from standard 4- to 5-hour three times weekly on-line HDF to 7–8 h sessions every other day with on-line HDF [20].

We observed that this change produced excellent clinical tolerance and patient acceptance, adequate social and occupational rehabilitation, better dialysis adequacy, remarkable improvement in nutritional status, regression of left ventricular hypertrophy, and good phosphate and hypertension control with a substantial reduction in the need for phosphate binders and antihypertensive medication.

Prospective, Randomized Ongoing On-Line Hemodiafiltration Studies

The year 2007 was instrumental in the development of on-line HDF in Catalonia since this treatment modality was promoted by the local government: the Catalonian Health Authorities gave an additional reimbursement for on-line HDF to dialysis care providers. The Catalonian Society of Nephrology promoted a prospective, randomized, open study to evaluate the potential benefits regarding patient survival of on-line HDF over standard hemodialysis: the '*Estudio de Supervivencia de Hemodiafiltración On-Line*' (ESHOL)'. This is an ongoing study that has enrolled 906 patients, 50% on high-flux hemodialysis and 50% on on-line HDF with post-dilutional infusion, with a follow-up period of 3 years [21]. The primary objective is survival. As the coordinator of this study, I had the opportunity to teach on-line HDF to more than 20 hospitals and dialysis centers through theoretical and practical sessions in 2007 and 2008. It was very rewarding to share our experience and interact with a large number of colleagues and nursing staff to assist in the implementation of this technique and help dispel any doubts that arose.

There are also several other ongoing multicenter, prospective randomized studies that may help to determine whether convective techniques are superior to hemodialysis or not. However, each of these studies has a different design (table 1).

An Italian multicenter study has enrolled 146 patients, of which 50% receive low-flux HD, 25% receive on-line HDF with pre-dilutional infusion, and 25% receive pre-dilutional hemofiltration. The follow-up is 2 years.

The Dutch Convective Transport Study (CONTRAST) aims to include 800 patients, 50% on low-flux HD, and 50% on post-dilutional on-line HDF. The monitoring period is 3 years and the primary objective is survival.

A French multicenter study aims to include 600 patients over 65 years of age, 50% on high-flux hemodialysis and 50% on post-dilutional on-line HDF. The monitoring period is 2 years and the primary goal is intradialytic tolerance.

Table 1. Some ongoing studies comparing on-line HDF and HD

	Italian study	French study	Contrast study	Turkish HDF study	ESHOL study
Country	Italy	France	Netherlands	Turkey	Catalonia, Spain
Design	RCT	RCT	RCT	RCT	RCT
Number	146	420	700	780	906
Baseline year	2004	2005	2004	2007	2007
Final year of study	2008	2010	2010	2010	2011
Groups compared	Pre-dilution HDF-OL/HF vs. low-flux HD 1:1:2	Post-dilution HDF-OL vs. high-flux HD 1: 1	Post-dilution HDF-OL vs. low-flux HD 1:1	Post-dilution HDF-OL vs. high-flux HD 1:1	Post-dilution HDF-OL vs. high-flux HD 1:1
Primary endpoint	Cardiovascular tolerance and blood pressure	Intradialytic tolerance	Mortality	Mortality and cardiovascular events	Mortality
Outcome	2 years	2 years	3 years	2 years	3 years

HD = Hemodialysis; HDF = hemodiafiltration; HF = hemofiltration; OL = on-line; RCT = randomized controlled trial.

A Turkish study aims to include 800 patients, 50% on high-flux hemodialysis and 50% on post-dilutional on-line HDF. The monitoring period is 2 years and the primary purpose is to evaluate cardiovascular morbidity and mortality.

Conclusions

In view of reports in the literature and our own experience, now is the time to switch to convective techniques [22]. Firstly, because technological development in water treatment and advances in dialysis machines, as well as the widespread use of synthetic high-flux dialyzers, make this a feasible proposition. Indeed, the latest generation of dialysis machines, known as therapeutic systems, are designed to work under convective conditions at all times using the dialysis fluid itself as the replacement solution. Secondly, we have listed the possible clinical benefits of these treatments and have found no published literature reporting any undesirable effects. We eagerly await receiving further scientific evidence from the ongoing multicenter studies.

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