Hemodiafiltration: A Mini Review

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Hemodialysis allows people with kidney failure to survive vital organ failure; however, most do not recover premorbid functional status. Despite early efforts focused on increased removal of small molecular weight solutes, high levels of morbidity and mortality persist due to the condition underlying kidney failure, comorbid medical conditions, and poor clearance of larger molecules. Early studies demonstrated that hemodiafiltration increases the removal of larger molecules through convective clearance. Recent studies have documented improvements in cardiovascular events, quality of life, and mortality. We review the mechanics of hemodiafiltration and the scientific data supporting improved outcomes.

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Introduction

Hemodialysis was developed for the treatment of the uremic syndrome caused by acute kidney injury by Dr Willem Kolff in Holland in 1943. Maintenance hemodialysis for chronic kidney disease became a practical reality with Dr Belding Scribner's shunt in Seattle in 1960. Practical realities limited the frequency and duration of hemodialysis treatments, leaving patients in a permanent state of controlled uremia.

When the kidneys function normally, they clear tens of thousands of different molecules which vary considerably in size, shape, and protein binding. To evaluate clearance by dialysis, these substances are divided based on molecular weight (MW): low MW solutes < 300 daltons (Da), middle MW solutes between 300 and 15,000 Da, and large MW solutes > 15,000 Da.[1] Initial efforts to identify the molecules responsible for the uremic syndrome concentrated on low MW solutes; however, the National Cooperative Dialysis Study (NCDS)[2] documented that, despite removal of most of the urea produced between dialysis treatments, patients receiving maintenance hemodialysis continued to have significant morbidity and mortality.

In more recent years, attention has focused on middle MW solutes, whose clearance by hemodialysis is limited because diffusion coefficients decrease rapidly with increasing molecular size.[3] High-flux hemodialysis membranes enhance the removal of larger molecules compared to low-flux membranes, but a significant survival benefit has not been consistently demonstrated.[4,5] Hemodiafiltration (HDF), developed in the 1980s, combines convective clearance with diffusive clearance, resulting in superior removal of larger molecules.[6]

Mechanics of Hemodiafiltration

Clearance

HDF provides diffusive clearance similar to hemodialysis, which uses the random movement of molecules related to thermal energy (Brownian motion) across a semipermeable membrane. Diffusive clearance of a given solute is directly proportional to the effective area of exchange while being inversely related to its size and the distance it has to travel. Clearance of a solute is reduced by plasma viscosity, protein binding, and molecular size. Viscosity increases progressively as blood passes through the dialyzer due to ultrafiltration (UF). In predilution HDF, fluid is infused before the blood reaches the dialyzer, decreasing the plasma viscosity while also reducing diffusive clearance. In postdilution HDF, the most common form of HDF, infusion of fluid after the dialyzer avoids dilution and enhances clearance compared with conventional hemodialysis, but UF leads to a greater rise in blood viscosity as it passes through the dialyzer compared with predilution HDF (Fig 1).[7]

HDF enhances convective clearance by adding substitution fluid into the bloodstream and increasing the UF rate above that required to remove excess fluid.[7] Convective clearance depends only on the rate of fluid flow and the sieving coefficient for the solute, which reflects the size of the membrane pores in relation to the size of the molecule. Fluid flow rates vary inversely with viscosity of blood, which is determined largely by hematocrit and body temperature. Achieving high UF rates requires high blood flow rates, generally at least 200 mL/min per 1.0 m^2 of dialyzer surface area.[9,10]

Studies have evaluated the differences in clearance for a variety of molecules with HDF compared with conventional hemodialysis. Small molecules like urea (60 Da) and creatinine (113 Da) are effectively cleared by both hemodialysis and HDF. High-volume HDF increases the clearance of small molecules compared with conventional hemodialysis; for example, with HDF volumes greater than 20 liters, Kt/V increases by 0.1-0.15. Large molecules like granulocyte-inhibiting protein I (28,000 Da), α1-microglobulin (33,000 Da), and α1-acid glycoprotein (44,100 Da) are poorly cleared by both hemodialysis and HDF. High-flux dialyzers enhance middle molecule clearance with hemodialysis when compared with low-flux dialyzers, but the clearance of middle molecules—including vitamin B_{12} (1,355 Da), inulin (5,200 Da), osteocalcin (5,800 Da), β_2-microglobulin (11,800 Da), leptin (16,000 Da), myoglobin (17,200 Da), prolactin (23,000 Da), and factor D (23,500 Da)—is significantly increased by HDF compared with hemodialysis.[11]

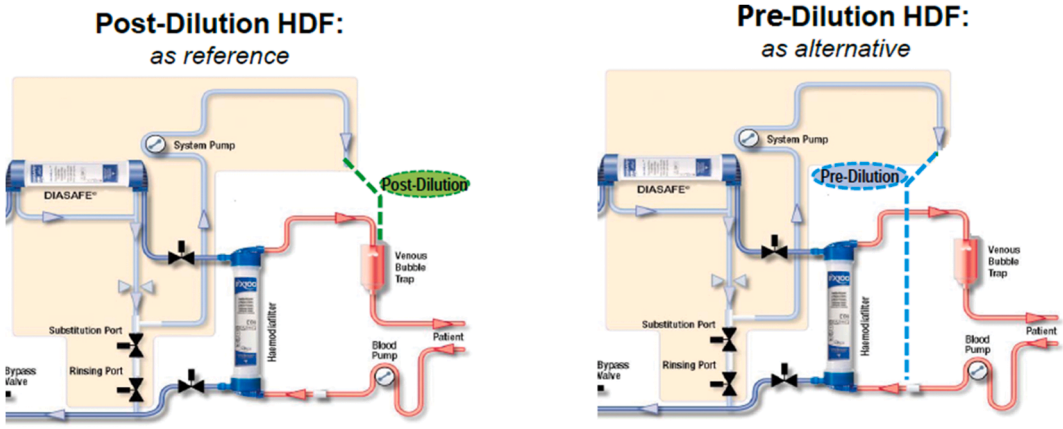

Figure 1. Dilution modes in hemodiafiltration. Abbreviation: HDF, hemodiafiltration. Released under a CC BY 3.0 license from Imamovic et al.[8]

Fluid Purity and Biocompatibility

HDF uses synthetic membranes with sterile, nonpyrogenic replacement fluid.[12] With online HDF, replacement fluid is produced from dialysate run through ultrafilters to remove solutes, bacteria, and endotoxins. The high UF rates result in protein-coating of the membrane, further increasing biocompatibility, but this also impairs membrane permeability.[12,13] Improved biocompatibility reduces inflammation, which improves management of malnutrition, anemia, and atherosclerosis.[14]

Dialyzer Selection

HDF employs high-flux membranes with a UF coefficient greater than 20 mL/h/mm Hg/m^2 and a sieving coefficient for β_2-microglobulin greater than 0.6 to enhance convective solute removal while minimizing albumin loss.[15] The dialyzer must withstand high transmembrane pressures resulting from large infusion volumes.[13]

Fluid Infusion Rates

Early versions of HDF used substitution fluid in prefilled bags, limiting the infusion volumes to less than 10 liters per session. Online preparation of substitution fluid allows for the generation of higher amounts of substitution fluid and high-volume HDF, leading to improved convective clearance while maintaining membrane permeability. HDF delivers a convection volume of at least 20% of blood volume processed.[15] In postdilution HDF, filtration fraction is typically limited to 30% due to hemoconcentration. Although predilution avoids this issue, higher flow rates are needed for equivalent convection volumes. Data from recent controlled trials have documented that the clinical benefits from postdilution HDF begin at convection volumes exceeding 23 liters per session.[6]

Anticoagulation

High UF volumes result in hemoconcentration, increasing the risk of blood clotting, so anticoagulation may be needed for successful HDF. Unfractionated heparin provides safe treatment and maintains adequate blood flow.[10]

HDF Machines and Regulatory Considerations

In 2017, nearly 300,000 patients worldwide received treatment by HDF with treatment numbers continuing to increase yearly. The patterns vary significantly depending on local regulations and health care policies. In 2017, more than 25% of European patients with kidney failure were treated by HDF, ranging from 0 in some countries to 76% in Switzerland[16]; in 2017 in Japan, the HDF share also rose to more than 25% after policy changes led to improved reimbursement for HDF.[17] In the United States, many barriers have contributed to the limited availability of HDF systems,[18] but US Food and Drug Administration 510(k) approval of Fresenius Medical Care's 5008X Hemodialysis System in 2024 is expected to lead to dramatic changes in access to HDF.[19]

Widespread uptake of HDF in the United States will have to overcome financial barriers in addition. HDF with online production of replacement fluid will be more costly than standard hemodialysis; the HDF treatments in the referenced clinical trials lasted at least 4 hours, so the average treatment duration will increase, bringing additional costs to the dialysis center. Financial feasibility will depend on reimbursement by the Medicare Prospective Payment System (PPS). To encourage uptake of innovative technology, the US Centers for Medicare & Medicaid Services (CMS) established the End-Stage Renal Disease (ESRD) PPS Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES) beginning January 1, 2020.[20] Eligible technologies must represent a "significant clinical improvement" in the diagnosis or treatment of Medicare beneficiaries. TPNIES establishes payment at 65% of the Medicare Administrative Contractor–determined price for a 2-year period.

For Fresenius' 5008X Hemodialysis System, a dialysis facility would pay 35% of the purchase price. Because there is no mechanism for additional reimbursement for the HDF treatment, the dialysis facility would have to

absorb that cost. These financial considerations will limit the use of HDF in the United States in most settings. Uptake may be more widespread at facilities participating in shared savings programs because of clinical data showing improved outcomes including lower rates of hospitalization and cardiovascular disease.

Clinical Outcomes of HDF Compared With Hemodialysis

Based on differential clearances, HDF has been hypothesized to provide clinical benefits, including better nutrition due to increased leptin clearance leading to improved appetite; anemia control due to improved response to erythropoietin with increased removal of medium- and large-sized mediators of inflammation; decreased cardiovascular events due to reduced inflammation; less intradialytic hypotension related to a thermal cooling effect from higher fluid infusion rates; reduced infectious complications due to increased clearance of degranulation inhibitory protein I (DIP I), granulocyte inhibitory protein II (GIP II), and factor D; and improved joint pain and reduced dialysis-related amyloidosis due to improved clearance of β_2-microglobulin.[9]

To assess for survival benefit with HDF, several clinical trials have compared the outcomes of HDF with standard hemodialysis; 3 were inconclusive (CONTRAST, Turkish OL-HDF, and FRENCHIE)[20-23]; the fourth (ESHOL) demonstrated reduced mortality with HDF.[24] Post hoc analysis of the Turkish OL-HDF study showed that patients treated with greater volumes of substitution fluid (>17.4 liters per session) had better cardiovascular and overall survival compared with the patients treated by high-flux hemodialysis.[22] A pooled analysis of the 4 clinical trials examined the relationship between convection volume and outcomes. After a median follow-up period of 2.5 years, online HDF reduced all-cause mortality by 14% and cardiovascular mortality by 23%. The greatest benefit was realized by patients receiving high convective volumes: greater than 23 liters per 1.73 m^2 body surface area.[25]

More recently, the CONVINCE trial,[26] a multinational, pragmatic, randomized clinical trial, evaluated the outcomes of prevalent patients for a primary outcome of all-cause mortality and secondary outcomes of cause-specific mortality, composite fatal and nonfatal cardiovascular events, kidney transplantation, and recurrent all-cause or infection-related hospitalizations. The groups were well-matched at baseline. Of the 1,360 patients randomized to high-dose HDF or high-flux hemodialysis, the median follow-up time was 30 months. In the HDF group, 92% of patients achieved the target volume of 23 ± 1 liters per session. Death occurred in 17.3% of the HDF group and 21.9% of the hemodialysis group (hazard ratio [HR], 0.75 [95% CI, 0.65-0.93]). Subgroup analysis showed differences in treatment effects by the presence of pre-existing cardiovascular disease and history of diabetes mellitus. Among the patients with a history of cardiovascular disease, the risk of death was similar in the 2 groups; among those without a history of cardiovascular disease, the risk of death was lower in the HDF group (HR, 0.58 [95% CI, 0.42-0.79]). There also was a lower risk of death among patients with no history of diabetes mellitus (HR, 0.65 [95% CI, 0.48-0.87]).

A metanalysis of the 5 trials showed a reduction in both all-cause mortality (HR, 0.84 [95% CI, 0.74-0.95]) and cardiovascular mortality (HR, 0.78 [95% CI, 0.64-0.98]) in the patients treated with HDF compared with hemodialysis.[27] A dose-dependent relationship with convective volume was also noted.

The CONVINCE trial also evaluated quality of life with HDF compared with hemodialysis using a survey of health-related quality of life with 8 domains: physical function, cognitive function, fatigue, sleep disturbance, anxiety, depression, pain interference, and social participation.[27,28] The response rate was 85%. Scores across all domains declined throughout the course of the study with a slower rate of decline noted in the HDF group, particularly for physical function, cognitive function, and social participation. Similarly, the FRENCHIE study[22] focused on intradialytic tolerance and demonstrated significantly less symptomatic intradialytic hypotension and muscle cramps with HDF. The overall health-related quality-of-life scores did not differ between the 2 groups.

Conclusion

Data from clinical trials support the hypothesis derived from basic science work: hemodiafiltration is associated with improved clinical outcomes compared with high-flux hemodialysis due to increased clearance of larger molecules. Patients in Europe and Japan have been afforded the advantages of HDF, but those in the United States have not due to unavailability and regulatory constraints. Introduction of Fresenius' 5008X Hemodialysis System holds promise for bringing HDF to the US market, but reimbursement constraints remain an obstacle to widespread use of HDF.

Article Information

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