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Hemodiafiltration in end-stage renal failure

Abstract

Patients suffering from end-stage renal failure who require renal replacement therapy have a high mortality rate. Despite attempts to improve dialysis therapy, such as increasing the frequency or efficiency of dialysis, there has been no significant progress in extending tlife expectancy of dialysis patients. In addition to hemodialysis, hemodiafiltration is an available form of renal replacement therapy. The studies available to date have not demonstrated an advantage of either method. Recently, the CONVINCE study was published, which showed a reduction in total mortality in patients undergoing hemodiafiltration. This article summarizes the current knowledge on the use of hemodiafiltration in patients with end-stage renal failure.

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INTRODUCTION

Life expectancy of patients with end-stage renal failure requiring renal replacement therapies is not high. The 5-year survival rate, according to the United States Renal Data System (USRDS) [1], is approximately 40% and is worse compared to prostate, breast, or colorectal cancer (only in lung and pancreatic cancer is survival lower). Despite attempts to improve dialysis therapy (appropriate frequency, efficiency, and use of improved dialysis membranes or high-flux dialyzers), no significant progress in extending life expectancy of dialysis patients has been observed [2].

DIFFERENCES BETWEEN HEMODIALYSIS AND HEMODIAFILTRATION

Hemodialysis (HD) [3] is a procedure designed to cleanse the blood of unnecessary metabolic products and the excess water that cannot be removed from the body due to abnormal renal function This procedure is based on the phenomenon of diffusion involving exchange of small-molecule substances across a semi-permeable membrane due to difference in concentration.

In the dialyzer, the patient's blood and the solution (called dialysate) are separated from each other by a semi-permeable membrane that has fine pores that allow only small molecules (such as urea and creatinine) to pass from the patient's blood into the dialysate, which is then removed from the body. Control of water metabolism is achieved by ultrafiltration, which occurs due to differences in hydrostatic pressures.

Hemofiltration and hemodiafiltration (HDF) use the phenomenon of convection to eliminate medium and large particles. Hemofiltration mainly involves the removal of water (and the substances dissolved in it) by convective transport with a hydrostatic pressure gradient on both sides of the filter membrane. This method allows large particles to be removed but is not as effective at removing smaller ones. The excess fluid that has been removed is replaced with a replacement fluid, with an electrolyte composition similar to plasma. It can be replaced before the dialyzer (predilution) or after the dialyzer (postdilution).

Hemodiafiltration is a combination of hemodialysis and hemofiltration, allowing the removal of medium and large molecules by convection (hemofiltration), as well as small molecules through the diffusion component (hemodialysis). Due to the large amount of fluid removed during ultrafiltration, to maintain the balance of water, the fluid deficiency must be supplemented intravenously as in hemofiltration.

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Do we have evidence to suggest that hemodiafiltration is more beneficial compared to hemodialysis?

Hemodiafiltration allows more toxins to be removed from the body (both small and large molecules), provides greater hemodynamic stability [4], and also, in patients on HDF, non-specific inflammation in the body is less severe [5], which should theoretically result in better outcomes for patients. However, do we have evidence that HDF is more beneficial in patients with end-stage renal failure than HD?

The results obtained in the studies conducted to date comparing hemodiafiltration and hemodialysis have not been conclusive. Until last year, 4 of the 5 randomized trials conducted (i.e. CONTRAST [5], THFDS [6], FRENCHIE [7], Locatelli et al. [8]), showed no reduction in total mortality in patients undergoing HDF compared to HD.

Only the ESHOL study [4] showed that compared with patients remaining on HD, patients on HDF had a 30% lower risk of total mortality (hazard ratio [HR] 0.70; 95% confidence interval [95% CI], 0.53–0.92; P = 0.01). This was mainly due to a lower risk of death from infectious complications (HR 0.45; 95% CI, 0.21–0.96; P = 0.03). In contrast, regarding mortality from cardiovascular disease (which remains the most common cause of death in dialysis patients), all the studies demonstrated no significant difference between patients on HDF and HD.

Admittedly, the aforementioned ESHOL study reported a 33% lower risk of death from cardiovascular causes, but these results did not meet the criteria for statistical significance (HR 0.67; 95% CI 0.44–1.02; P = 0.06). However, it is worth mentioning some limitations of this study. First, approximately 10 percent of patients did not complete the study due to inadequate blood flow; second, there were different transplantation rates between groups or differences between the number of patients lost to follow-up between study groups.

The results from these studies were analyzed together in the paper by Peters et al. [9], who showed that HDF was associated with a 14% reduction in total mortality and a 23% reduced risk of cardiovascular death compared to HD. However, this is not an original article or a randomized trial but a meta-analysis, so the results should be approached with caution. Therefore, these studies did not provide clear evidence that hemodiafiltration is more beneficial. Consequently, in the United States, the Food and Drug Administration (FDA) did not even approve HDF as a renal replacement therapy, which led to the launching of a study under the acronym CONVINCE [10].

The CONVINCE study recruited 1,360 patients from 61 centers located in eight European countries, where patients were randomized in a 1:1 ratio to an HD or HDF group. Adult patients with end-stage renal failure who had been on hemodialysis for at least three months and who were highly likely to undergo effective high-flow HDF (> 23 L) were included. According to the study protocol, HDF had to last at least 4 hours, with blood flow values of min. 350–400 mL/min and the convection volume (the sum of the substitution volume and the ultrafiltrate volume) should be at least 23 L. Total mortality was taken as the primary endpoint, while mortality due to cardiovascular and infectious causes, repeat hospital admissions, renal transplantation, and the occurrence of cardiovascular events were secondary endpoints.

The CONVINCE trial showed a 23% reduction in total mortality with HDF, mainly as a result of a reduced number of infectious complications. On the other hand, there was no significant effect on reducing cardiovascular mortality.

How does the relevance of this study compare with other studies conducted in cardiology, endocrinology, or nephrology, among others? The NNT (number needed to treat) index, i.e. how many patients we need to treat to prevent 1 death, indicates the effectiveness of the chosen therapy. In the DAPA-CKD study (dapagliflozin), it was 48 [11], in PARADIGM-HF [12] (sacubitril/valsartan) it was 38, in LEADER [13] (liraglutide) it was 71 and in CONVINCE it is 21, which is a great success, especially in such a demanding population as dialysis patients.

WHAT DO WE NEED FOR SUCCESSFUL HEMODIAFILTRATION?

To perform a successful hemodiafiltration procedure, it is important to achieve an adequate convection volume of min. 23 L/session in the postdilution option. This target should be adapted individually to the body surface area (the larger the body surface area, the higher the volume of substitution).

The three most important determinants of convection volumes are [10, 14]:

Table 1. Comparison of hemodialysis and hemodiafiltration

	Hemodialysis	Hemodiafiltration
Mechanism of action	Diffusion	Diffusion and convection
Size of particles to be removed	Fine particles	Fine, medium and large particles
Hemodynamic stability of patients	Smaller	Greater
Duration of treatment	Shorter	Longer
Blood flow rate (BFR)	Smaller	Greater 350–450 mL/min.
Replacement of the removed excess water	–	Pre/postdilution substitution

a. Blood flow rate (BFR) — target between 350–450 mL/min. Usually, at the start of HDF, the BFR is 300 mL/min, and it is recommended to increase it by 50 mL/min during subsequent sessions until the target values are reached provided that the patient tolerates it well. This requires good vascular access to ensure adequate blood supply, which makes it unlikely that many patients with a dialysis catheter will qualify for this treatment method. It also requires the use of thicker needles, usually 15 G or thicker.
b. filtration fraction (FF) — is the ratio of the convection volume to the blood flow rate multiplied by the time and expressed as a percentage (the result should be multiplied by 100%). It usually starts with FF 25% and then increases by 2% during each subsequent treatment until FF 33% is reached.
c. Dialysis time — extending the duration of the procedure to a minimum of 4 hours.

Furthermore, to perform a proper HDF procedure, it is necessary to have the right equipment. Currently, most of the devices used for HD also allow for HDF to be performed. These include, for example, the Fresenius 5008 CoreDiax, Fresenius 6008 CARE-system, INFOMED HF440, and D Braun Dialoq+. Regarding the choice of dialyzers, standard high-flux dialyzers are used, i.e. those used in HD (e.g. FX60) with a surface area of 1.6–2.5 m^2. Therapy should start with a dialyzer with a smaller surface area and then, with good tolerance, the surface area should be increased to maximize convection volume and blood purification. Other parameters that the dialyzer should meet are the ultrafiltration coefficient > 20 ml/hr/mmHg/m^2, capillary diameter 200 μm, sieving coefficient (Sc) β_2-microglobulin > 0.6, and albumin < 0.001.

What if, despite using these modifications, we still cannot obtain an adequate convection volume? In that case, it is worth checking the hematocrit because when the hematocrit is greater than 35%, the risk of blood clotting in the dialyzer increases. In this case, it should be checked if the dose of erythropoiesis-stimulating factors is not too high. Notably, in HDF a higher dose of low molecular weight heparin is usually needed compared to HD.

CONCLUSIONS

The CONVINCE study, performed on a large number of patients, showed unequivocally a reduction in total mortality in patients on HDF *vs.* HD. Its results are promising and make a convincing case for the widest possible use of this renal replacement therapy in dialysis stations [10].

A randomized, multicentre H4RT trial [11] is currently underway to compare the effectiveness (both clinical effectiveness and cost-effectiveness) of high-dose hemodiafiltration and high-flux hemodialysis. The study group is expected to be 1550 patients, and the primary endpoint is expected to be non-cancer-related mortality and the rate of hospital admissions related to cardiovascular events and infections. Hopefully, the results of this study will confirm the superiority of HDF over HD obtained in the ESHOL and CONVINCE trials and hemodiafiltration will be a widely used therapeutic modality in patients with end-stage renal disease.

Conflict of interest:
The authors report no conflict of interest.

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