Survival Benefit with Hemodiafiltration

Are We Convinced, and If So, What Might Be the Mechanism?

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Blankestijn and colleagues recently published a pragmatic, multinational, randomized controlled trial involving 1360 patients with kidney failure randomly assigned to high-flux hemodialysis or high-dose hemodiafiltration (with at least 23 L of convective clearance per session).[1] The investigators reported a reduction in deaths (118 [17.3%] in the hemodiafiltration group versus 148 [21.9%] in the hemodialysis group), with a mortality hazard ratio of 0.77 (95% confidence interval, 0.65 to 0.93) over a median follow-up of 30 months.

Predefined subgroups included age group, biologic sex, history of cardiovascular disease, diabetes residual urinary output (<1000 or ≥1000 ml/d), vascular access type, and dialysis vintage. The mortality difference was most pronounced in patients older than 65 years. Mortality difference between hemodiafiltration and hemodialysis was absent in those with preexisting cardiovascular disease but was marked and significant in patients without preexisting cardiovascular disease. Mortality difference was greater in patients without diabetes compared with patients with diabetes. The survival benefit of hemodiafiltration tended to be greater in women compared with men.

Secondary outcomes included hospitalizations and cause-specific mortality (cardiovascular and infectious). The hospitalizations were not reduced in the hemodiafiltration group. The mean relative hemodiafiltration:hemodialysis mortality hazard ratios for cardiovascular and noncardiovascular mortality were 0.81 (0.49 to 1.33) and 0.76 (0.59 to 0.98), respectively. This trend was in the opposite direction to what was found in a previous combinatorial analysis of four randomized hemodiafiltration versus hemodialysis trials,[2] where the survival benefit of hemodiafiltration seemed to be more pronounced with cardiovascular mortality. Mortality due to infectious causes seemed to be most different, with the relative hemodiafiltration:hemodialysis mortality hazard ratio being 0.69 (0.49 to 0.96). More than half of the infection-related deaths were associated with coronavirus disease (COVID); however, relative death rates due to infection with hemodiafiltration versus hemodialysis were similar when COVID-related deaths were excluded.

Postdilution hemodiafiltration using a relatively high replacement fluid infusion rate was targeted from the outset, and mean delivered convection volume during follow-up averaged 25.3 L per session. A previous combinatorial study of four randomized trials suggested that a survival benefit from hemodiafiltration versus hemodialysis, if indeed such existed, was more pronounced in patients receiving higher replacement fluid volumes and that a minimum replacement fluid level of 23 L per session needed to be present to affect survival substantially.[2] One potential source of bias was that patients receiving high-volume hemodiafiltration needed to have accesses that supported higher blood flow rates and so may have been healthier at the time of randomization. The Comparison of High-Dose Haemodiafiltration with High Flux Haemodialysis (CONVINCE) trial reduced the chance for this bias by limiting entry to patients who were judged able to achieve a fluid replacement rate of over 23 L/per session.

If high-volume hemodiafiltration does indeed affect survival so substantially over a relatively brief (30 months median) follow-up period, then what might be the mechanism?

With high-flux membranes, the β-2-microglobulin reduction ratio over a 4-hour dialysis session is commonly in the range of 55%–70%, and this tends to be an underestimate because of the opposing effect of protein hemoconcentration.[3] Hemodiafiltration increases the removal all solutes, but the increase in large molecule removal is greatest such that the β-2-microglobulin reduction ratio with high replacement fluid volumes is commonly in the 70%–85% range, usually approximately 15%–25% points higher compared with the reduction ratio achieved with hemodialysis. Typically, predialysis serum β-2-microglobulin levels in patients with minimal residual function being dialyzed 3/wk with low-flux membranes are in the range of 30–50 mg/L, with normal values being approximately 0.70–1.8 mg/L. In patients being treated with 3/wk high-flux dialysis, predialysis β-2-microglobulin values typically measure approximately 25–32 mg/L. Despite the higher β-2-microglobulin reduction ratios with hemodiafiltration, predialysis β-2-microglobulin values in patients treated with hemodiafiltration are only approximately 10%–15% lower than in those treated with high-flux hemodialysis and usually remain well above 20 mg/L, a value that still is more than ten-fold higher than levels in patients with normal kidney function. Uremic toxins of even higher molecular weights than β-2-microglobulin,

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in the range of 15–45 kDa, may also contribute to uremic toxicity.[4] Hemodiafiltration may lower predialysis and time-averaged serum levels of these heavier molecules to a greater extent compared with high-flux hemodialysis than the 10%–15% lowering of predialysis serum β-2-microglobulin. In addition, hemodiafiltration has been demonstrated to lower predialysis serum levels of protein-bound toxins, such as indoxyl sulfate and p-cresyl sulfate compared with high-flux hemodialysis, though only by 5%–15%.[5] The extent to which slight to modest lowering of predialysis serum levels of such novel candidate uremic toxins might affect patient survival remains an area of active investigation.[6]

The one previous randomized comparison of hemodiafiltration versus hemodialysis that showed the greatest hemodiafiltration-related survival benefit was the Estudio de Supervivencia de Hemodiafiltración (ESHOL) study from Spain. In that study, there was no difference in predialysis β-2-microglobulin levels in the hemodiafiltration versus hemodialysis group during follow-up.[7] In the CONVINCE trial, neither β-2-microglobulin reduction ratio nor predialysis β-2-microglobulin levels were measured, although they perhaps still could be from stored specimens. One has to somehow reconcile the observed survival benefit seen with hemodiafiltration with the mechanistic hypothesis that hemodiafiltration exerts its survival benefit by increased removal of large molecular weight toxins, given the relatively small reduction of predialysis serum β-2-microglobulin levels with hemodiafiltration compared with high-flux hemodialysis.[8]

Are there other possible explanations for a survival benefit for hemodiafiltration? One hypothesis has to do with extracorporeal circuit temperature. In the ESHOL hemodiafiltration versus hemodialysis trial, there was a markedly reduced incidence of intradialytic hypotension (IDH) in the hemodiafiltration group. IDH occurrence is strongly associated with mortality. In some but not all studies, IDH occurrence is reduced in patients dialyzed with cool dialysate, and the use of high volumes of replacement fluid in hemodiafiltration can lower temperatures in the extracorporeal circuit somewhat, although the extent of this effect has not been properly studied. Arguing against the hypothesis of a thermal effect on survival operating through reduced IDH are the negative results of the multicenter pragmatic Personalised Cooler Dialysate for Patients Receiving Maintenance Haemodialysis (MyTEMP) trial in which a survival benefit of cooled dialysis solution could not be demonstrated and in which there were no differences in BP with standard versus cooled dialysis solution.[9] There is no information provided in the CONVINCE trial manuscript nor in the appendix regarding any measurements related to either IDH or thermal balance.

Mortality rate in hemodialysis patients is related to ultrafiltration rate, and it is possible that hemodiafiltration, by perhaps altering sodium balance, might result in a lower ultrafiltration rate, thereby leading to a lower mortality. This is an unlikely mechanism for a survival benefit of hemodiafiltration versus hemodialysis, as no marked differences in ultrafiltration rate were reported in any of the previous randomized trials. No information is provided in CONVINCE regarding ultrafiltration rate. The median treatment session length was close to 245 minutes in both arms, suggesting that any difference in ultrafiltration rate was unlikely (Supplemental Table 2, data appendix).

One mechanism relating to improved survival with hemodiafiltration in CONVINCE might be that the dialysis solution used in the hemodiafiltration arm was more pure than dialysis solution provided during hemodialysis treatments due to additional membrane purification of the dialysis solution in hemodiafiltration mode. Cleaner dialysis solution might result in less inflammation. However, it seems that the same degree of dialysis solution purification was used in both arms of the CONVINCE trial, which would seem to reject this particular explanation of benefit. In addition, CONVINCE did report predialysis serum C-reactive protein levels during follow-up (Supplemental Table 2, data appendix), and the mean values in serum C-reactive protein were almost identical in the two arms.

Completing the list of potential mechanisms for a hemodiafiltration benefit, one might postulate that hemodiafiltration resulted in better maintenance of residual kidney function than hemodialysis. Data on residual kidney function were available in only 11% of patients in CONVINCE, so this particular potential mechanism cannot be adequately assessed from the available data. Median vintage of patients entering the CONVINCE study at baseline was close to 3 years, so it is not likely that many enrolled patients had substantial amounts of residual kidney function. Finally, it is possible that the benefit of hemodiafiltration on survival may be multifactorial, as proposed by Canaud *et al.*[10]

In summary, the authors are to be congratulated for successfully conducting this study during a period when health care delivery was severely affected during the COVID-19 pandemic. The survival benefit that was found in favor of hemodiafiltration over hemodialysis is substantial and is consistent with the magnitude of benefit found previously in a combinatorial study of four previous randomized hemodiafiltration versus hemodialysis comparisons. However, a mechanistic explanation for this apparent hemodiafiltration survival benefit continues to be elusive.

Disclosures

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