Intensive Hemodialysis Fails to Reduce Plasma Levels of Uremic Solutes

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In this issue of the *Clinical Journal of the American Society of Nephrology*, Kalim *et al.* (1) report that extending the duration of in-center hemodialysis had little effect on the plasma levels of small solutes. They used mass spectrometry to compare solute levels over 1 year in 20 patients maintained on conventional thrice weekly hemodialysis and 33 patients who switched from conventional hemodialysis to thrice weekly nocturnal hemodialysis. The average treatment time was nearly doubled in the patients on nocturnal hemodialysis (21 versus 11 hours). This large increase in treatment time, however, had little overall effect on the levels of 164 solutes measured. Of particular note, the increase in treatment time did not significantly reduce the levels of any of the 25 solutes that had previously been classified as uremic on the basis of their accumulation in patients with kidney failure.

The measurements of Kalim *et al.* (1) cast an interesting light on previous studies of extending treatment duration. Extending treatment duration has regularly been found to facilitate control of extracellular fluid volume, BP, and phosphate levels (2). Other benefits, however, have proven more difficult to identify. Observational data from a large provider showed that 2-year mortality was 25% lower in patients receiving thrice weekly nocturnal hemodialysis than in patients receiving conventional treatment (3). The authors noted, however, that selection bias may have contributed to this benefit. Also, a recent randomized trial found that extending the average weekly treatment time from 14 to 22 hours over 1 year did not improve patients' quality of life (4). The data in the work by Kalim *et al.* (1) suggest that large increases in treatment time may not provide the benefit that we would hope for, because they do not significantly reduce the plasma levels of uremic solutes.

Limited reduction in uremic solute levels may also account for the limited benefits observed in other trials of intensified kidney replacement therapy. Current treatment standards are based heavily on the results of the Hemodialysis (HEMO) Study, which randomized patients to receive "high-dose" dialysis with an average single-pool Kt/V_{urea} of 1.73 or "standard" dialysis with an average single-pool Kt/V_{urea} of 1.32 (5). Clinical reports from the HEMO Study showed that "high-dose" dialysis had no discernible effect on mortality, hospitalization, nutrition, or health-related quality of life. A subsequent analysis of stored plasma samples found that levels of nine uremic solutes were, on average, only 7% lower in patients receiving "high-dose" dialysis than in patients receiving "standard" dialysis (5). The daily arm of the Frequent Hemodialysis Network Trial compared conventional three-times weekly hemodialysis with more frequent treatment combined with a longer weekly treatment time. Intensive treatment improved BP and phosphate control but had little, if any, effect on physical or cognitive function (6). A subsequent metabolomic analysis revealed that increasing treatment frequency from three to six times per week and treatment time from 11 to 15 hours resulted in an average reduction of only 15% in the levels of 107 uremic solutes (7). Trials designed to increase the removal of large uremic solutes by convective clearance present a similar picture. In two of three randomized trials, mortality was not reduced in patients receiving hemodiafiltration compared with patients receiving hemodialysis. Additionally, plasma levels of the representative large solute β_2-microglobulin were not reduced in proportion to the estimated increases in its clearance (8).

Why have all of these more intensive treatment regimens achieved relatively small reductions in solute levels? We believe that there are three main reasons that apply in different proportions to different solutes (8,9). The first is the intermittency of treatment. Solutes are removed during treatment and reaccumulate between treatments. If most of a solute is removed during conventional treatment, extending the treatment duration or increasing the clearance cannot remove much more. Also, the solute level at the beginning of the next treatment will be nearly the same as with conventional treatment. Examination of urea levels in the HEMO Study illustrates this point. "Standard" dialysis reduced the urea level by 66% during each treatment. Therefore, average pretreatment urea levels were only 9% lower when Kt/V_{urea} was increased by 30% by providing a higher dialytic clearance and longer treatment time in the "high-dose" patients. Additionally, if a solute's reduction ratio during each treatment is greater than that of urea, increasing dialytic clearance and/or treatment time will result in an even smaller reduction in the solute's pretreatment plasma level.

A second reason for the failure of solute levels to fall as much as we would hope with intensified treatment is the presence of nondialytic clearance. Such nondialytic clearance can be provided by residual native kidney function or outside the kidney. Because it operates continuously, a nondialytic clearance that is only a small portion of the dialytic clearance can have a large effect on plasma solute levels (9). The importance of

nondialytic clearance has been shown most clearly for β_2-microglobulin and other low molecular weight proteins. The HEMO Study compared "high-flux" dialysis, providing a β_2-microglobulin clearance of 34 ml/min, with "low-flux" dialysis, providing a β_2-microglobulin clearance of only 3.4 ml/min (8). Despite the nearly tenfold higher dialytic clearance, plasma β_2-microglobulin levels were only 20% lower in the "high-flux" patients than in the "low-flux" patients (10). The failure of an increased dialytic clearance to achieve a greater reduction in β_2-microglobulin levels was attributable largely to the presence of a continuously operating nondialytic clearance of approximately 3 ml/min, which is responsible for the majority of β_2-microglobulin removal from the circulation, even in patients receiving "high-flux" dialysis. This nondialytic clearance has also greatly limited the reduction in plasma β_2-microglobulin levels that can be achieved by using hemodiafiltration to further increase β_2-microglobulin clearances (8).

A third reason for the failure of solute levels to fall with intensified treatment, we believe, may be increases in solute generation. Here, we are on softer ground, because solute generation has been much less extensively studied than solute removal. Reports of the plasma levels of *p*-cresol sulfate in patients on dialysis, however, provide evidence that solute generation can vary with solute removal; *p*-cresol sulfate is the sulfate conjugate of *p*-cresol that is formed by colon microbes from the amino acids tyrosine and phenylalanine. Plasma levels of *p*-cresol sulfate have been found to remain the same when its removal is increased by a variety of kidney replacement therapies, suggesting that *p*-cresol sulfate generation increases in proportion to its removal (8).

As noted by Kalim *et al.* (1), blood flow rates and thus presumably, the clearances of some solutes were reduced when treatment time was increased in their patients receiving nocturnal dialysis. This limitation to solute removal with extended treatment duration can easily be remedied. The three limitations to lowering solute levels by increasing treatment intensity that are described above, however, are harder to overcome. Not only do they apply in different proportions to different solutes, but also, they can act in concert. The limited reduction in β_2-microglobulin levels seen in large trials of hemodiafiltration can, for instance, be accounted for by the presence of nondialytic β_2-microglobulin clearance combined with limitations imposed by the intermittency of treatment on the effects of increasing clearance (8). Also, the failure of Kalim *et al.* (1) to see any reduction in the levels of uremic solutes with known high reduction ratios during conventional treatment could be accounted for by a modest increase in their generation as well as by a reduction in their dialytic clearance attributable to the reduction in blood flow during treatment.

The authors appropriately note other factors that may have influenced solute levels in their study. The patients on nocturnal hemodialysis were of younger vintage than the patients on conventional hemodialysis, and loss of residual function in the patients on nocturnal hemodialysis could have offset increased solute removal by extended treatment duration. The different time of day at which pretreatment blood samples were obtained may have influenced levels of metabolites, such as amino acids, although we doubt that it had a significant effect on the levels of uremic waste solutes.

Where do we go from here? More intensive kidney replacement treatments have not provided the benefits hoped for. The findings of Kalim *et al.* (1) add to evidence suggesting that the intensive treatments so far tested have provided limited benefit, because they have achieved limited reduction in uremic solute levels. The factors that prevent solute levels from falling with more intensive treatment include the intermittency of treatment, nondialytic solute clearance, and increased solute generation. Different means will be required to lower the levels of individual solutes. We need to know which solutes are toxic to design better treatments. If we knew which solutes to target, we could explore means to limit their generation or increase their nondialytic clearance as well as increase their removal by kidney replacement therapy.

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Disclosures

None.

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See related article, "Extended Duration Nocturnal Hemodialysis and Changes in Plasma Metabolite Profiles," on pages 436–444.