Isothermic Dialysis-a New Panacea for Intradialytic Hypertension?

Maintenance hemodialysis (HD) has emerged as a life-sustaining therapy for end-stage renal disease (ESRD) patients. Recent clinical research in this field has focused on patho-physiological processes causing procedural complications. One such complication is intradialytic hypertension (IDH), which is defined as an intradialytic or post-dialytic rise in systolic blood pressure (SBP) by ≥10 mmHg over predialysis readings.[1] Large cohort studies have reported an incidence of at least one episode of IDH in 10% of chronic HD patients with 9% of such individuals having persisting IDH over a span of 6 months.[1] Despite controversy surrounding the accuracy or reliability of intradialytic SBP readings, observational data indicate an increased risk for all cause and cardiovascular death in patients developing IDH, behoving us to minimize this complication.[2] Risk factors identified for IDH on the basis of both observational and interventional data include chronic volume overload, positive dialysate-patient sodium gradient, and increased intradialytic peripheral vascular resistance from release of potent vasoconstrictors such as endothelin-1.[1,3,4] Other postulated mechanisms are given in Table 1.

In this issue, Veerappan *et al*. present their data on a single center randomized cross-over study that adds yet another dimension to our knowledge on IDH by proposing that primary heat gain during standard HD may be contributory.[5] The authors subjected 60 chronic HD patients to two sessions of standard hemodialysis (SHD) with dialysate temperature fixed at 37°C and two sessions of isothermic hemodialysis (IHD) in varying random sequences to primarily study the incidence of IDH. IHD was delivered by matching dialysate temperature to axillary temperature measured at the start of dialysis. Data collected from 240 HD sessions showed significantly lesser incidence of IDH in IHD (37%) as compared to SHD (66%).[5] Other benefits of IHD included significantly lower incidence of intradialytic hypotension (12% vs. 38%) and lower intradialytic mean SBP and BP variability.[5] *Post hoc* classification of patients as "responders" defined as those with ≥5 mmHg drop in SBP with IHD as against the "non-responders" showed no differences in inter dialytic fluid gain and total ultrafiltration (UF) per HD session between the groups.[5]

Table 1: Major proposed mechanisms for intradialytic hypertension (Adapted from Reference 1)

Volume overload
Increased arterial stiffness
Activation of sympathetic nervous system
Activation of renin-angiotensin-aldosterone system
Endothelial dysfunction
Net sodium gain during dialysis
High dialysate calcium
Erythropoiesis stimulating agents (intravenous more than subcutaneous route)
Dialytic removal of anti-hypertensive agents

Cooled dialysis refers to either a fixed lowering of dialysate temperature to 0.5–1.0°C below patient's core temperature (CT) or to "isothermic" dialysis where CT is kept constant using a biofeedback temperature-control device.[6] It has been previously shown that intradialytic hypotension may be caused by elevation in CT during dialysis that leads to compensatory peripheral vasodilatation and that "isothermic" dialysis can effectively reduce this complication.[6] The underlying mechanism for the benefit of cooled dialysis is that it prevents the rise in CT during SHD from either a positive heat transfer from extra-corporeal circuit especially when set dialysate temperature is higher than actual CT or by blocking the phenomena of diminished peripheral heat loss due to cutaneous vasoconstriction in response to intravascular volume contraction during ultrafitration.[6] The study by Veerappan *et al*. is probably the first to suggest that heat stress generated from a fixed 37°C dialysate can lead to IDH.[5] The authors speculate that this could be from paradoxical vasoconstriction in response to twin situations of heat stress and hypovolemia as shown in normal human experiments.[5,7] Regardless of the mechanisms involved, the impressive reduction in incidence of IDH could be generalizable to a high-risk population because study subjects had substantial interdialytic weight gains (~3.4–3.5 kg) with high average UF rate of around 12.4 ml/kg/h making them particularly vulnerable to such complications.[5]

A few caveats in the study deserve mention. Firstly, in the absence of a proper biofeedback temperature device to establish isothermal conditions, it is difficult to say with precision if constant CT was maintained throughout the so-called IHD sessions. Because dialysate temperature in the IHD arm was matched to CT only at the beginning of the HD session, it is quite possible for UF to induce a rise in CT later during dialysis leading to peripheral vasodilatation and subsequent drop in BP in patients prone to IDH. Although this should increase the incidence of intradialytic hypotension, this was not the case. Secondly, data on patient-dialysate sodium gradient are missing, so it is difficult to exclude the effects of negative sodium gradient (patient serum Na higher than dialysate Na) on primary outcomes. Thirdly, details of anti-hypertensive drugs in responders/non-responders is missing. This is relevant since certain anti-hypertensives such as carvedilol have recently been shown to lower the incidence of

IDH.[2] Finally, given the small sample size and *post-hoc* categorization of responders/non-responders, it is difficult to interpret similar UF or fluid gains between the two groups as suggestive of an independent effect of dialysate temperature modulation on the incidence of IDH.

Notwithstanding many questions raised by the study of Veerappan *et al*., the impressive results obtained with a simple intervention of matching patient's body temperature with dialysate temperature at start of dialysis in terms of lowering the incidence of IDH could be a major step in improving clinical outcomes in hemodialysis patients if confirmed in larger studies.

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