Published in final edited form as:

Semin Dial. 2017 November ; 30(6): 509–517. doi:10.1111/sdi.12629.

Osmolality and Blood Pressure Stability During Hemodialysis

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Abstract

Homeostatic regulation of plasma osmolality (POsm) is critical for normal cellular function in humans. Arginine vasopressin (AVP) is the major hormone responsible for the maintenance of POsm and acts to promote renal water retention in conditions of increased POsm. However, AVP also exerts pressor effects, and its release can be stimulated by the development of effective arterial blood volume depletion. Patients with end-stage renal disease on hemodialysis, particularly those with minimal or no residual renal function, have impaired ability to regulate water retention in response to AVP. While hemodialysis can assist with this task, patients are subject to relatively rapid shifts in volume and electrolytes during the procedure. This can result in the development of transient osmotic gradients that lead to the movement of water from the extracellular to the intracellular space. Hypotension may result – both as a consequence of water movement out of the intravascular compartment, but also from impaired AVP release and inadequate vascular tone. In this review we explore the evidence for POsm changes during hemodialysis, associations with adverse outcomes, and methods to minimize the rapidity of changes in POsm in an effort to reduce patient symptoms and minimize intra-dialytic hypotension.

Keywords

Osmolality; Intra-dialytic hypotension; dialysate sodium; hemodialysis; ESRD

Evolutionary Basis of Osmoregulation

“Earth’s turbulent history has made us what we are.”

This quote from Homer Smith in his book ‘From Fish to Philosopher’ encapsulates the importance of environmental influences on the evolution of life on Earth.¹ The regulation of salt and water balance (osmoregulation) was perhaps one of the most important of these events, allowing primitive organisms to move from saline-rich seas to more dilute environments. While the primitive kidney was mainly concerned with the elimination of metabolic waste that could not undergo simple diffusion, the transition to more dilute environments necessitated that the kidney assume a central role in the elimination of water

(while retaining sodium chloride). Indeed, the study of comparative physiology has illuminated our understanding of how different species regulate their own internal environment, which Claude Bernard famously described as the “*milieu intérieur*”.² Maintaining the constancy of the *milieu intérieur* was critical to the development of advanced tissues, such as nerves and muscles, in the vertebrate organisms that antedated humans.

Fast-forward in time to humans and the kidney has maintained its central role in the regulation of water homeostasis. While osmoregulation is critical for the normal functioning of basic cellular reactions, the evolution of renal salt and water handling has endowed the kidney with the primary responsibility for the control of extracellular volume, and consequently blood pressure. It should therefore come as no surprise that these homeostatic mechanisms become fragile and may even fail in patients with advanced kidney disease, leading to numerous adverse sequelae that include volume overload and hypertension. Furthermore, when such patients are treated with hemodialysis (which attempts to control salt and water balance on average three times per week), perturbations may become even more apparent. The goal of this review is to examine the pathophysiology of osmoregulation in hemodialysis patients and the association of hemodialysis-induced changes in plasma osmolality (POsm) with important clinical outcomes.

Determinants of Plasma Osmolality

Total body water in humans is distributed between the extracellular and intracellular compartments, each having a predominant solute that serves to hold water within it – sodium for the extracellular compartment and potassium for the intracellular compartment. The intravascular space comprises approximately 20% of the extracellular compartment.³ Water movement between the intracellular and extracellular compartments (including the intravascular space) is therefore primarily determined by osmotic forces. In general, charged solutes such as sodium and potassium do not move freely across cell membranes and are therefore mostly restricted to their respective compartments (effective osmoles). On the other hand, lipid-soluble molecules such as urea are classically considered as ineffective osmoles, as they can freely diffuse across cell membranes.³

Changes in POsm are detected by osmoreceptors in the hypothalamus, which mediate their response via the control of thirst and release of arginine vasopressin (AVP).⁴ For example, in normal subjects, the development of hyperosmolality stimulates thirst (promoting ingestion of hypotonic fluid) and the release of AVP. The latter binds to V2 receptors on the basolateral surface of principal cells in the distal convoluted tubule, initiating an intracellular signaling cascade that results in insertion of aquaporin 2 (AQP2) channels into the apical membrane. This facilitates the subsequent retention of water down the medullary concentrating gradient. The net result of these responses (renal water retention and ingestion of hypotonic fluid) is the lowering of POsm and the maintenance of osmotic equilibrium. In the setting of ESRD, patients with little or no residual renal function are unable to mount this renal response to AVP, and are reliant on the HD procedure for control of solute and water balance.

While the primary determinant of greater AVP release is higher POsm, the development of a significant decline in effective arterial blood volume is also a potent stimulus for AVP release. This response strives to preserve and defend adequate blood pressure, and is partially achieved by renal retention of water (in an effort to boost blood volume), but also via the action of AVP on V1a receptors of the vascular endothelium (where it exerts a pressor effect).^{5,6} In fact, in cases of profound decrements in effective arterial blood volume (>10%), the preservation of blood pressure may take precedence over the maintenance of a 'normal' POsm. In the case of oligo-anuric ESRD patients on hemodialysis, although baseline AVP levels tend to be higher compared with healthy controls, several studies^{7,8} have reported minimal changes in AVP concentrations in response to HD, which may predispose to an impaired ability to prevent intra-dialytic hypotension.

Measurement of Plasma Osmolality

Osmolality may be defined as the concentration of a solution based on the number of osmoles of solute per kilogram of solvent. There are numerous formulae available that can provide an estimate of the POsm, with one of the more common examples used in clinical practice as follows:

$$\text{Calculated POsm (mOsm/kg)} = 2 * (\text{Plasma Na in mmol/L}) + \text{Plasma Urea Nitrogen (in mg/dL)} / 2.8 + \text{Plasma Glucose (in mg/dL)} / 18^{9,10}$$

Although the majority of the POsm is determined by the plasma sodium concentration (PNa), it is important to remember that the PNa is primarily a function of the ratio of solute and water, and does not provide an accurate assessment of volume status. In the case of oligo-anuric dialysis patients, the presence of hyponatremia is most commonly due to ingestion of hypotonic fluids. While the so-called normal range for POsm osmolality is 275–290 mOsm/kg in the general (non-HD) population, patients with ESRD on hemodialysis typically have higher pre-dialysis values in the range of 291 to 339 mOsm/kg.^{11–14} This phenomenon is largely driven by elevated blood urea nitrogen concentrations (BUN) in such patients.

One must be cognizant that the formula above only estimates the POsm ('calculated' POsm). The exact 'measured' POsm is typically determined by the technique of freezing point depression in modern laboratories. The difference between the measured and calculated osmolalities is referred to as the osmolar gap, and is typically <10 mOsm/Kg in normal circumstances. The osmolar gap is frequently higher in HD patients, suggesting the presence of additional osmotically active molecules, and tends to close somewhat during the HD session.¹⁵

Osmolality Changes During Hemodialysis

Contemporary hemodialysis is highly efficient in the removal of urea and other small molecules from the blood. Indeed, the removal of urea has been studied extensively for decades as a method to assess the efficiency or adequacy of dialysis treatments. POsm has been reported to decrease by up to 33 mOsm/kg over the course of a HD treatment,^{11–14} and

is thought to be primarily due to the removal of urea. Although classically viewed as an 'ineffective osmole', several lines of evidence suggest that the rapid clearance of urea from the blood during hemodialysis may lead to the generation of temporary osmotic gradients,^{16–19} such that water has a favorable osmotic gradient to move from the extracellular to the intracellular space. These shifts have been postulated to account for many of the symptoms of the so-called dialysis disequilibrium syndrome,²⁰ and may also predispose to the development of intra-dialytic hypotension (IDH) via the resultant decline in intravascular volume.^{21,22} As outlined earlier, another potential mechanism relates to the relative inability of ESRD patients to increase circulating levels of AVP during hemodialysis.^{7,12} This phenomenon is perhaps a result of the relatively rapid decline in POsm that occurs via the clearance of urea and other osmotically active substances, thereby predisposing to the development of hypotension via insufficient maintenance of vascular tone.

Osmolality Changes and Adverse Outcomes

Despite the pathophysiologic rationale described, there are limited data that directly examine measured intra-dialytic changes in POsm with adverse clinical outcomes. In a prior analysis by our group, we reported that higher pre-dialysis calculated osmolality was independently associated with 10% greater odds of experiencing a hypotensive event (OR 1.10; 95% CI, 1.05–1.15) in adult patients undergoing thrice-weekly maintenance hemodialysis. When the independent contributions of pre-dialysis plasma sodium, BUN and glucose were analyzed we found that higher BUN and glucose, but lower plasma sodium, were associated with a greater magnitude of intra-dialytic SBP decline.²³ In this setting, we hypothesized that hyponatremia in oligo-anuric ESRD patients is more likely a marker for comorbid conditions that predispose to the development of IDH, and/or may identify those with greater inter-dialytic fluid consumption.

Similarly, in a post-hoc analysis of the HEMO Study, we found that those randomized to the higher target Kt/V arm (a surrogate for greater urea clearance) had a greater odds of developing IDH (OR 1.12; 95% CI 1.01–1.25) compared with the those in the standard Kt/V arm.²⁴ Within the session length constraints of the HEMO study, the higher target Kt/V implied greater rapidity of urea removal, adding further support to the role of rapid changes in POsm in the pathogenesis of IDH. Further evidence supporting the association of perturbations in the POsm-AVP axis with IDH can be extrapolated from studies of interventions that were designed to: 1) minimize the magnitude of the intra-dialytic decline in POsm (e.g. administration of hypertonic fluids or the use of higher dialysate sodium prescriptions); or 2) directly administer exogenous vasopressin.

Interventions to Minimize Intra-Dialytic Osmolality Decline

Infusion of Hyperosmolar Solutions - Mannitol

One of the earliest reports of mannitol use came from Hagstam et al. in 1969. They reported a double-blind trial where six patients were administered 1g/kg mannitol, 0.5 g/kg mannitol, placebo (0.9 g% glucose) or placebo (0.18 g% glucose) in random order. During the sessions with mannitol, POsm declined by 17 mOsm/kg on average, compared with 26 mOsm/kg in the placebo arm. There were no reported changes in blood pressure, but there were

significantly fewer cramps in the sessions where mannitol was given. The plasma mannitol concentration was noted to decrease by 50% within an average of three days between each session.²⁵ Similar findings were noted by Rodrigo et al. who reported that the decline in POsm was 10 mOsm/kg with regular HD and 4 mOsm/kg with the use of 1g/kg mannitol.²⁶

Henrich et al. expanded on these findings by performing an experimental HD protocol to reduce body weight by 2–3% during 2-hour sessions under various experimental conditions in six chronic normotensive HD patients. During regular HD POsm fell by 20 mOsm/kg, but only fell by 3 mOsm/kg in those that received hypertonic mannitol, while mean blood pressure fell from 90 to 75 mmHg in the regular HD sessions, but only from 89 to 83 mmHg in those receiving hypertonic mannitol. It is also interesting to note that the use of isolated ultrafiltration (UF) resulted in minimal decrements in POsm (309 to 306 mOsm/kg) and mean blood pressure (89 to 86 mmHg).²⁷

In another study of six pediatric patients prone to IDH (mean age 12 years), Hothi et al. reported that the use of mannitol vs. not was associated with a 56% reduction in the frequency of intra-dialytic symptoms (abdominal pain, cramps, headaches, loss of consciousness or change in behavior),²⁸ with similar findings from a prospective review of 506 treatments from ten patients.²⁹ Furthermore, Battaglia et al. examined the association of HD with changes in brain neuronal excitability (by intra-cortical facilitation), noting that the increase in ICF with regular HD could be attenuated by the administration of hypertonic mannitol.³⁰

Our group examined 102 patients initiating hemodialysis at two major academic teaching hospitals (one of which routinely administered mannitol; the other did not) in an observational cohort study. We noted that the administration of hypertonic mannitol was associated with a 5 mmHg higher nadir SBP during HD and a lower adjusted odds of experiencing hypotension (OR 0.50; 95% CI 0.29–0.83).³¹ Caveats of this study included the small sample, observational nature of the study and the potential for a center effect; strengths include the reduced likelihood of confounding by indication, as the use of mannitol vs. not was based on protocol, as opposed to individual prescribing practices.

Infusion of Hyperosmolar Solutions – Glucose and Saline

Some early studies also report on the hemodynamic changes associated with hypertonic glucose infusions. For example, Mostert et al. performed detailed physiological experiments on 15 HD patients following infusion of 50% glucose (100mL over 5 minutes followed by 40 drops per minute). They noted a sharp rise in measured POsm that was accompanied by an increase in SBP and cardiac output. Of note these experiments were not carried out during HD itself.³²

More recently Shimuzi et al. performed a mechanistic study to evaluate the hemodynamic effects of infusing hypertonic saline (20 mL 10%), hypertonic glucose (20 mL 50%), normal saline (200 mL 0.9%) or physiologic doses of vasopressin. With respect to hypertonic glucose they found that POsm increased from 293 mOsm/kg at baseline to 300 mOsm/kg after three minutes ($P<0.001$); plasma AVP increased from 3.7 to 6.1 pg/mL ($P=0.05$); while SBP increased from 92 to 100 mmHg ($P=0.004$). The change in plasma volume was

approximately 3.7%, which the authors did not feel was sufficient to fully explain the magnitude of the observed blood pressure rise. Of note, similar results were obtained with the hypertonic saline infusion.¹¹ Another study by this group found that the magnitude of rise in endogenous AVP and resultant changes in blood pressure is proportional to the rate of infusion, with mean arterial pressure increasing by 15 mmHg when hypertonic saline was infused over 2 minutes versus a rise of 7 mmHg when infused over 5 minutes.³³

Higher Dialysate Sodium

Manipulation of the dialysate sodium concentration was one of the first approaches used by clinicians to minimize symptoms of dialysis disequilibrium³⁴ and subsequently to minimize IDH. Delivery of a hyperosmolar dialysate can be achieved by using a fixed higher DNa (typically >140 mmol/L) or by the use of sodium modeling algorithms, whereby the DNa starts higher (e.g. >145 mmol/L) and then decreases during the course of the HD session.

Many studies have reported beneficial effects of higher DNa in terms of fewer adverse patient symptoms and reduced frequency of IDH.^{35–38} Conversely, several studies report associations of higher DNa with thirst, greater IDWG and higher blood pressure.^{39–41} However, in terms of ‘hard’ clinical outcomes, select observational studies have noted that the association of higher DNa with mortality appears to differ according to the pre-dialysis PNa, such that higher DNa actually appears to be protective for patients with lower pre-dialysis PNa.^{42–44} One plausible explanation for this observation may be that lower PNa identifies sicker patients that may be a greater risk of intra-dialytic hemodynamic instability. Indeed, despite PNa being a major determinant POsm, our prior work suggests that lower pre-dialysis PNa is also associated with greater risk of IDH.²³ A more expansive review of DNa prescriptions is beyond the scope of the present article, but such reviews are available.^{45,46}

Exogenous vasopressin infusion

Based on the pathophysiology described above, some investigators have bypassed the use of hyperosmolar infusions to stimulate endogenous vasopressin production, in favor of direct administration of exogenous forms of vasopressin. In the mechanistic study by Shimuzi et al, a dose-dependent relationship between the administration of exogenous AVP (2mU/min in the low-dose arm and 4mU/min in the higher dose arm) and increased mean arterial pressure was identified – mean SBP increased from 94 mmHg at baseline to 99 mmHg after 30 minutes in the lower-dose group, and from 90 mmHg to 104 mmHg in the higher-dose group. The magnitude of blood pressure changes observed with lower-dose infusions was of similar magnitude to those obtained with the use of hypertonic saline and glucose.⁴⁷

In a different study, van Der Zee et al. performed a randomized double-blind study of continuous vasopressin infusion (0.3 mU/kg/min) compared with placebo in 22 non-hypotension prone patients. In this protocol the target ultrafiltration volume was increased by 0.5 kg above the baseline prescription in order to probe hemodynamic fluctuations. Compared with the placebo group, the decline in SBP was significantly less (16 vs. 32 mmHg; P=0.008) and there were fewer hypotensive events (9% vs. 64%; P=0.02) in those that received the vasopressin infusion.⁴⁸

In a somewhat novel approach, Lindberg et al. examined the use of intra-nasal lysine vasopressin in six IDH-prone patients in a double-blind cross-over study over a one-week period (two sprays in each nostril twice daily), reporting a reduction in the frequency of IDH (0.9 episodes vs. 1.5 episodes), higher intra-dialytic mean blood pressure at 90 minutes (82 vs. 77 mmHg; $P<0.05$) and lower requirement for administration of saline to treat low blood pressure events (155 vs. 280 mLs; $P<0.05$).⁴⁹

Isolated Ultrafiltration

Isolated ultrafiltration (UF) is a convection-based modality of volume removal⁵⁰ that is often used for HD patients that are profoundly hypervolemic or hemodynamically tenuous. Isolated UF does not require the use of dialysate fluid (diffusion) and therefore the ultrafiltrate is essentially isotonic to the patient's plasma. For example, in the study of six normotensive patients by Henrich et al., volume removal of 2–3% of body weight was performed over a two-hour period to probe for BP changes - the isolated UF protocol achieved the greatest decrease in body weight (3.2%) and, as expected, there were no significant changes in POsm, BUN, PNa or creatinine. Furthermore, there were minimal changes in mean upright BP measurements from pre- to post-procedure (91 to 86 mmHg; $P=NS$).²⁷

Reports from Rodriguez et al. also support these findings – in a study of 18 patients assigned to various target UF goals, they reported no significant changes in POsm. However, they did note that the rate of UF was proportional to the decline in mean arterial pressure and with increases in plasma oncotic pressure in their experimental protocols. They hypothesized that overly rapid UF, despite an increase in plasma oncotic pressure, may outpace refilling from the intracellular compartments and thereby predispose to hypotension.⁵¹ However, when UF rates were similar using isolated UF and UF with HD, Fleming et al. found similar rates of blood volume decline with removal of 0.6L volume, but still noted less hypotension with isolated UF (drop in mean BP of 10 vs. 18 mmHg; $P<0.05$).⁵² These findings, therefore, provide further support for the hypothesis that the perceived hemodynamic benefits of isolated UF may be partially related to the mitigation of rapid changes in POsm.

Feedback Mechanisms

In an effort to minimize adverse effects during HD, there has been considerable interest in the use of biofeedback mechanisms, whereby live monitoring of the changes in a chosen biomarker allows instantaneous alterations in the dialysate prescription. For practical and financial reasons, many of these studies have utilized online measurement of dialysate conductivity (given its linear association with sodium concentration),⁵³ as opposed to repeated measurements of specific electrolytes, or indeed POsm. For example, Selby et al. compared standard HD (dialysate conductivity of 13.6 mS/cm) with biofeedback HD (dialysate conductivity automatically adjusted within the limits of 13.0 and 14.0 mS/cm) in eight IDH-prone patients in a crossover fashion (one week per arm). During monitored sessions after a week of each therapy, biofeedback HD had a lower rate of IDH (12 vs. 24 episodes) and fewer new regional wall motion abnormalities, as assessed by echocardiographic analysis (23 vs 42; OR 1.8 [95%CI 1.1–3.0]).⁵⁴

Similar findings in IDH-prone patients have been reported by other groups.^{55–58} Selby et al. subsequently examined ten stable HD patients in a longer randomized crossover study. The standard HD group underwent progressive lowering of the dialysate conductivity from 13.6 to 13.4 to 13.2 mS/cm over six weeks, while the intervention arm were prescribed a target plasma conductivity by the end of the treatment (13.7, then 13.6 then 13.5 mS/cm). In contrast to their earlier study, there were no significant differences in rates of IDH between each arm and no differences in thirst scores, which the authors felt may have been partially attributable to the inclusion of only non-IDH prone patients.⁵⁹

In an effort to better understand the potential mechanisms by which biofeedback HD may be promote intra-dialytic blood pressure stability in select individuals, Ettema et al. performed a randomized crossover study of 15 chronic HD patients that were prone to the development of IDH. Patients randomly received regular HD (fixed dialysate conductivity 13.8 mS/cm) vs. Hemocontrol HD (variable dialysate conductivity with limits of 13.6 to 14.0 mS/cm) for one session each, during which plasma vasopressin concentrations were measured at multiple time points. Compared with the standard HD arm, there was a trend towards less SBP decline in the biofeedback arm (27 vs. 35 mmHg; $P=0.08$) and fewer episodes of IDH (5 vs. 0; $P=0.04$). This was accompanied by an almost two-fold increase in plasma vasopressin at 30 minutes into the biofeedback session, compared with a non-significant increase in the standard HD arm. Of note, these changes occurred early in the treatment, when UF rates with biofeedback treatments were most pronounced.⁶⁰

In summary, although the studies mentioned above utilize technology that senses and alters conductivity (as opposed to osmolality), the net effect is somewhat similar – higher dialysate conductivity (mediated by higher DNa) earlier in the HD treatment leads to less decline in POsm, perhaps increased vasopressin release, and ultimately improved intra-dialytic hemodynamic stability.

Conclusion

In recent years there has been renewed interest in the role of the dialysate prescription in relation to inter- and intra-dialytic blood pressure control. There are several lines of evidence to support an association of greater osmolality decline and impaired/inadequate vasopressin release with the development of IDH. Numerous interventions to minimize the decline in POsm (or to augment vasopressin release) are available, but their widespread adoption has been limited by associated side effects, e.g. inter-dialytic hypertension and weight gain with higher dialysate sodium. In fact, based largely on observational evidence, several experts have promoted lowering of the ‘standard’ dialysate sodium prescription because of these concerns.⁶¹ Conversely, others have urged caution in this regard given the association with greater risk of IDH and evidence for increased mortality for select individuals.⁶² Clearly, adequately powered clinical trials examining hard endpoints are urgently needed in this regard.

In terms of changes in POsm, it is probable that the rate of decline is of paramount importance, with slower rates of change allowing for more rapid equilibration between the intra- and extra-cellular spaces. A relatively simplistic approach to reduce the rate of POsm

decline (avoiding the use of higher dialysate sodium or other hyperosmolar solutions) may be to incrementally increase blood and dialysate flow over the first hour of treatment (while increasing overall dialysis session length to ensure adequate clearance). This may provide several additional benefits in terms of lower ultrafiltration rates, greater small and middle molecule clearance, and improved volume control. However, within the confines of the model of outpatient thrice-weekly HD, combined with patient resistance to longer treatments, this approach continues to face an uphill challenge.

The association of changes in POsm with patient symptoms and hemodynamic stability were recognized early in the history of dialysis therapy. Renewed interest in these pathophysiological pathways holds much promise for future research aimed at developing safe and effective interventions for patient care. As new protocols are developed by those interested in preventing IDH, it may be fruitful to consider the role of POsm changes and to focus early proof-of-concept recruitment efforts on patients at highest risk of such complications.

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Table 1

Selected studies of interventions designed to promote intra-dialytic hemodynamic stability.

Author (Year)	Patient Characteristics	Study design	Outcomes		Comments
			IDH	Cramps/Symptoms	
Hypertonic Mannitol					
Hagstam, 1969	-N=6 prevalent patients -Age range 25–59 -Twice weekly HD -DNa 127 mmol/L; acetate 30 mmol/L	Double blind, randomized, crossover trial of 4 protocols (3 wks/arm): I - 1g/kg mannitol; 0.9 g% glucose II - 0.5g/kg mannitol; 0.9 g% glucose III - 0.9 g% glucose IV - 1.8 g% glucose	NA	I- 17% cramps II- 28% cramps III- 33% cramps IV- 33% cramps	- Small N - Twice weekly HD - Comorbidities unknown - Acetate dialysate
Rodrigo, 1977	-N=16 prevalent patients -Mean age 30 yrs - 6 hr sessions -DNa 135 mmol/L; acetate 35 mmol/L	Nonrandomized, non-blinded; 4 sequential arms (1 session/arm) I – Mannitol 1g/kg + High glucose dialysate (717 mg/dL) II - Mannitol 1g/kg + Low glucose (274 mg/dL) III – High glucose (717 mg/dL) IV – Low glucose (274 mg/dL)	NA	Reduction in symptoms from 67% to 10%	- Small N - Comorbidities unknown - Acetate dialysate - Non-randomized - Some patients did not complete all four protocols
Henrich, 1980	-N=6 prevalent pts -All male -Mean age 59 yrs	Unclear if randomized; 5 arms (1 session/arm) I- Regular HD II- Isolated UF III- Isokalaemic HD IV – 25% mannitol, 0.16 g/kg/hr V – Isotonic 5% mannitol	Supine to standing BP fell from 90 to 75 mmHg with regular HD sessions, and 89 to 83 mmHg with hypertonic mannitol	NA	- Small N - Comorbidities unknown - Details of dialysate prescription unknown
Hothi, 2009	-N=6 pediatric pts -Mean age 12 yrs -3 or 4 HD/week -Na modeling for all	Open-label, uncontrolled (8 mo) I- Mannitol 1g/kg II- Sequential UF/HD III- Midodrine	44% reduced odds of IDH/ intervention with mannitol vs. none	56% reduced odds of symptoms with mannitol vs. none	- Small N - One pt had disproportionate number of events - Non-randomized - No control group
Battaglia, 2005	-N=36 -Sub-study of 8 HD patients -10 CKD, 10 transplant; 8 chronic HD and 8 chronic PD -Mean age 58 yrs	Double-blind, cross-over with one-wk washout (1 session/arm) I - 125 ml of 10% mannitol every hr II - equal volume of isotonic saline	NA	Post HD increase in intra-cortical facilitation; the magnitude was reduced by infusion of mannitol	- Sub-study of larger protocol - Short timeframe - Surrogate outcome of intra-cortical facilitation
Hypertonic Glucose or Saline					
Shimuzi, 2008	-N=42 -Mean age 66 yrs -Qb 200 mL/min -Qd 500 mL/min -4 hr sessions	Randomized, 4 interventions (one session/arm; no diabetes in protocol II) I – 10% saline 20 mL/5 mins II – 50% glucose 20 mL/2 mins III – 0.9% saline 200 mL – over 2 mins IV – AVP infusion; low-dose 10 mU bolus then 2mL/min for 20 mins; high-	I – SBP: 92 to 99 mmHg after 10 mins II – SBP: 92 to 100 mmHg after 3 mins III – SBP: 92 to 104 mmHg after 3 mins	NA	- Limited information on comorbidities - Single session per patient - Low Qb and Qd

Author (Year)	Patient Characteristics	Study design	Outcomes		Comments
			IDH	Cramps/Symptoms	
		dose 20 mU bolus then 4mU/min for 20 mins	IV – SBP:94 to 100 mmHg after 5 mins (low-dose); 90 to 107 mmHg (high-dose)		
Exogenous vasopressin					
Shimizu, 2008	-N=42 -Mean age 66 yrs -Qb 200 mL/min -Qd 500 mL/min -4 hr sessions	IV – AVP infusion; low-dose 10 mU bolus then 2mU/min for 20 mins; high-dose 20 mU bolus then 4mU/min for 20 mins	IV – SBP increased - 94 to 100 mmHg after 5 mins (low-dose); 90 to 107 mmHg (high-dose)	NA	- Limited information on comorbidities - Single session per patient - Low Qb and Qd
Van der Zee, 2007	-N=22 non-hypotension prone patients -Mean age 57.5 yrs -Qb 300–400 mL/min -Qd 600 mL/min -4 hr sessions	Randomized, double-blind, placebo-controlled (1 session/arm) I – 0.3 mU/kg/min vasopressin infusion II – 0.9% saline infusion	Maximal decline from pre-HD SBP was 34 mmHg with placebo vs. 16 mmHg with vasopressin (P=0.008) Less IDH (9% vs. 64%; P=0.02)	NA	- Small N - Limited information on comorbidities - Single session per patient
Lindberg, 1990	-N=6 hypotension-prone -Mean age 58 yrs -Qb 200–300 mL/min -Qd 500mL/min -3.5–4.5 hr sessions -DNa 140 mmol/L	Double-blind, randomized, cross-over (1 wk/arm) I – Intranasal lysine vasopressin twice daily (one hr pre-HD) II – Intranasal saline twice daily	MAP at 90 mins 82 mmHg (vasopressin) vs 77 mmHg (placebo) (P<0.05) Less IDH (MAP < 70mmHg) inactive arm (0.9 vs. 1.5; p<0.05)	NA	- Small N - Variable treatment of IDH – some with saline, others with salt-poor albumin - Low Qb and Qd - Short duration on each protocol
Isolated Ultrafiltration					
Henrich, 1980	-N=6 prevalent patients -All male -Mean age 59 yrs	Unclear if randomized; 5 arms, 1 session/arm I- Regular HD II- Isolated UF III- Isokalemic HD IV – 25% mannitol, 0.16 g/kg/hr V – Isotonic 5% mannitol	Supine to standing BP fell from 90 to 75 mmHg (HD), 89 to 86 mmHg (isolated UF)	NA	- Small N - Comorbidities unknown - Details of dialysate prescription unknown
Fleming, 1988	-N=10 -Median age 47 yrs -Qb 200–250 mL/min -Qd 500 mL/min -Cuprophane membrane -DNa 140 mmol/L; acetate 37 mmol/L	Protocol involved: - Isolated UF (600 mL removed over 30 mins) - Reinfusion of the 600 mL UF - UF + HD (600 mL removed over 30 mins)	Nadir BP 96 vs. 83 mmHg (isolated UF vs. UF + HD)	NA	- Small N - Short duration on each protocol - Incident and prevalent patients
Biofeedback					
Selby, 2006	-N=8 hypotensive prone -Mean age 68 yrs -Qb 250–450 -Qd 500 -Low flux dialyzers -IK bath - Dialysate temp 37 C	Crossover (1 wk/arm) I – dialysate conductivity 13.6 mS/cm II- automatic conductivity adjustment	Less IDH with biofeedback (12 vs. 24; IDH = SBP <90 mmHg or 40% drop with symptoms)	NA	- Small N - Low flux dialyzer and use of IK bath - Short duration on each protocol

Author (Year)	Patient Characteristics	Study design	Outcomes		Comments
			IDH	Cramps/Symptoms	
Selby, 2007	-N=10 non-IDH prone -Mean age 66.5 yrs -Qb 250–460 -Qd 500 -Low flux dialyzers -IK bath -Dialysate temperature 37 C	Crossover (8 weeks per arm) I- standard thrice-weekly HD. Dialysate conductivity lowered by 0.2 mS/cm from 13.6 mS/cm every 2 wks to 13.2 mS/cm II –end-dialysis prescribed plasma conductivity lowered every two weeks from 13.7 mS/cm to 13.5 mS/cm	No significant difference between standard and biofeedback HD at lowest settings in pre- (138 vs 142 mmHg), intra- (128 vs 124 mmHg), or post-SBP (127 vs 125 mmHg) measurements No difference in rates of IDH	No change in thirst scores	- Small N - Low flux dialyzer and use of 1 K bath - Stable patients - Short duration on each protocol
Ettema, 2013	-N=15 IDH-prone patients -Mean age 56 yrs -Qb 250–380 mL/min -Qd 500–700 mL/min -Low flux dialyzers -Fixed dialysate temp of 36.0 or 36.5 C	Randomized, crossover study (1 session/arm) I – Standard HD dialysate conductivity 13.9 mS/cm II- Intervention conductivity limits of 13.6 to 14.0 mS/cm	Maximal SBP decrease: 36 mmHg (standard HD) vs 27 mmHg (intervention, P=0.08) More IDH in standard HD (5 vs 0; P=0.04)	NA	- Small N - Low flux dialyzer - Short duration on each protocol