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REVIEW

Prevention of Intradialytic Hypotension in Hemodialysis Patients: Current Challenges and Future Prospects

Seyed Mehrdad Hamrahian[1], Salem Vilayet[2], Johann Herberth[2,3], Tibor Fülöp[2,3]

[1]Department of Medicine - Nephrology, Thomas Jefferson University, Philadelphia, PA, USA; [2]Department of Medicine - Division of Nephrology, Medical University of South Carolina, Charleston, SC, USA; [3]Medicine Services, Ralph H. Johnson VA Medical Center, Charleston, SC, USA

Correspondence: Tibor Fülöp, Department of Medicine - Division of Nephrology, Medical University of South Carolina, 96 Jonathan Lucas Street, Charleston, SC, 29525, USA, Tel +1 843 792-4123, Fax +1 843 792-2995, Email tiborfulop.nephro@gmail.com; fulopt@musc.edu

Abstract: Intradialytic hypotension, defined as rapid decrease in systolic blood pressure of greater than or equal to 20 mmHg or in mean arterial pressure of greater than or equal to 10 mmHg that results in end-organ ischemia and requires countermeasures such as ultrafiltration reduction or saline infusion to increase blood pressure to improve patient's symptoms, is a known complication of hemodialysis and is associated with several potential adverse outcomes. Its pathogenesis is complex and involves both patient-related factors such as age and comorbidities, as well as factors related to the dialysis prescription itself. Key factors include the need for volume removal during hemodialysis and a suboptimal vascular response which compromises the ability to compensate for acute intravascular volume loss. Inadequate vascular refill, incorrect assessment or unaccounted changes of target weight, acute illnesses and medication interference are further potential contributors. Intradialytic hypotension can lead to compromised tissue perfusion and end-organ damage, both acutely and over time, resulting in repetitive injuries. To address these problems, a careful assessment of subjective symptoms, minimizing interdialytic weight gains, individualizing dialysis prescription and adjusting the dialysis procedure based on patients' risk factors can mitigate negative outcomes.

Keywords: end-stage renal disease, dialysis, hemodialysis, hypotension, ultrafiltration

Introduction

Chronic kidney disease (CKD) is a significant global public health concern that often leads to end-stage renal disease (ESRD), requiring dialysis treatment or kidney transplantation.[1] Although the incidence of ESRD is reported to have plateaued in high-income countries, patient time spent receiving dialysis treatment is increasing due to longer patient survival on dialysis combined with limited availability of organ donors for the preferred modality of kidney transplantation.[2–4] CKD and ESRD are often accompanied by hypertension, which increases in prevalence as glomerular filtration rate (GFR) declines.[5] With the exception of specific comorbidities such as end-stage heart failure or advanced liver disease, practically all patients on hemodialysis (HD) have elevated blood pressure. This phenomenon is particularly prevalent prior to initiation of a dialysis session.[6,7] While blood pressure monitoring during dialysis treatment is occurring primarily for safety reasons, the value of these measurements is limited for describing the burden of hypertension in-between treatments. Intradialytic hypotension (IDH) is a frequently observed complication of intermittent hemodialysis because relatively short treatment times necessitate rapid volume removal of excess fluid gains. IDH bears a broad overlap with intravascular hypovolemia that is also characterized by hypotension during treatment. Preventive measures can potentially reduce patient stress during HD treatment sessions, thus minimizing the potential risk of vascular access failure and associated cardiovascular mortality;[8] even subtle asymptomatic blood pressure drops during HD treatment are potentially associated with significant end organ ischemia.[9] The goal of this review is to provide a concise overview of IDH emphasizing its relevance to practicing clinicians.

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Definition of Intra-Hemodialysis Hypotension

The incidence of IDH has been reported to vary between 5% and 40% in different ESRD patient populations.[10,11] This wide range is in part due to the lack of data collection secondary to the absence of randomized controlled trials and lack of consensus on the definition of IDH among relevant organizations.[12–15] In general, IDH is characterized by a rapid decrease in systolic blood pressure of greater than or equal to 20 mmHg and/or in mean arterial pressure (MAP) of greater than or equal to 10 mm Hg that results in end-organ ischemia and requires countermeasures such as ultrafiltration reduction or saline infusion to increase BP, to improve patient's symptoms. However, it should be noted that the correlation between blood pressure changes and clinical symptoms is poor, and some patients may exhibit signs of intravascular hypovolemia without a qualifying drop in blood pressure. Occasionally, a paradoxical rise in blood pressure may even be observed when physiologic compensatory mechanisms are vigorous.

Pathophysiology of Intra Hemodialysis Hypotension

Blood pressure monitoring during dialysis is performed primarily for safety reasons to alert care personnel for impending hemodynamic destabilization. The pathogenesis of IDH involves an interaction between ultrafiltration rate (UFR), cardiac output (CO), vascular resistance and the ability to refill volume from the extravascular space. Risk is increased by non-modifiable patient-related factors such as age and comorbidities like diabetes mellitus or cardiac diseases. Dialysis prescription-related risk factors include high UFR and dialysate temperature. In general, patients on intermittent HD are more sensitive to large shifts of volume during the relative short HD treatment time. The decline in relative blood volume induced by high UFR and limited plasma volume refill from the interstitial compartment plays a significant role in the pathogenesis of IDH.[16] Volume removal during dialysis triggers cardiopulmonary receptors in the atria and baroreceptors in the aortic arch and carotid sinuses. Volume depletion results in activation of sympathetic nervous system (SNS) and stimulation of the renin-angiotensin-aldosterone system.[17] Activation of SNS increases cardiac venous return by reducing venous capacitance in the splanchnic and cutaneous circulations in support of the central circulation.[18] Simultaneously, there is an increase in heart rate, cardiac contractility and peripheral vascular resistance. The presence of diastolic dysfunction, a common finding in ESRD patient populations, increases the risk of IDH if cardiac venous return is compromised.[19] Elevated levels of pro-inflammatory cytokines (TNF-α and IL-1β) were reported in IDH and correlated with excessive BP drop during dialysis in vulnerable patients.[20] Reduced myocardial perfusion at the end of dialysis as a result of volume removal can lead to left ventricular dysfunction increasing the future risk of IDH,[21] while high UFR-induced IDH itself is described as a predictor for cardiac remodeling.[22]

Risk Factors of Intra Hemodialysis Hypotension

High Inter-Dialytic Weight Gain (IDWG)

Excessive fluid gains between HD sessions will lead to volume overload and increase the risk of mortality in ESRD.[23] Although IDWG is associated with a relatively modest increase in plasma volume, most of the combined salt and water fluid gain is sequestered in the extravascular and extracellular spaces. Additional intake of free water will also increase the intracellular fluid compartment volume because it affects the entire water compartment. During dialysis, net fluid removal reduces the central filling pressure and leads to a decrease in CO.[24] High IDWG requires higher UFR, which can overwhelm the physiologic compensatory mechanisms and increase the risk of IDH.[25] Furthermore, rapid UFR of >13 mL/kg/h is described to increase cardiovascular morbidity and mortality.[26] Even lower UFR can induce IDH in diabetics due to slow plasma refill and decreased vasoconstriction secondary to autonomic dysfunction.[27] In general, starting UF at a higher rate and then slowly decreasing it over the course of the dialysis session is associated with the lower risk of IDH.[28]

Serum Osmolality

Another potential factor contributing to IDH associated with short HD treatment is the rapid clearance of urea. This can result in decreased plasma osmolality and the formation of transient osmotic gradients causing water to shift from the intravascular space to the intracellular and interstitial spaces.[29] The risk is higher in patients with higher pre-dialysis calculated plasma osmolality undergoing shorter treatment.[30] Furthermore, it is possible that trends in the last few decades such as using larger surface filters and larger blood- and counter-current flow rates may have further exacerbated this phenomenon. In this context, sodium also plays an important role as the major component of plasma tonicity. Utilization of higher dialysate sodium without sodium profiling could potentially prevent rapid reduction in plasma osmolality and reduce the osmotic fluid shifts.[31] Additionally, isolated UF that removes isotonic fluids without diffusive clearance maintains BP stability compared to usual HD.[32] This strategy can be combined with regular HD in the special patient population presenting with high IDWG without a significantly abnormal pre-treatment elevated blood urea nitrogen level.

Electrolyte Abnormalities

Relatively large bicarbonate influx and overcorrection of metabolic acidosis may contribute to intradialytic blood pressure drop.[33,34] This phenomenon may broadly overlap with acute, intradialytic drop of ionized calcium and clinical complaints of leg cramps during dialysis.[34–36] Preventive measures may include mitigating predialysis acidosis with exogenous bicarbonate supplementation,[37,38] but an effect on IDH has not been studied.

Decreased Cardiac Output

CKD is an independent non-modifiable risk factor for cardiovascular disease (CVD).[39] In ESRD patients, CVD-related morbidity and mortality are high even among younger individuals.[40] Multiple manifestations of cardiac diseases including low ejection fraction, diastolic dysfunction, valvular diseases, and arrhythmias are highly prevalent among ESRD patients. Heart failure and loss of contractility predispose the patient to IDH due to decreased cardiac output.[41] Frequent episodes of IDH can also cause myocardial stunning resulting in progressive heart failure and increased risk of cardiovascular mortality.[42]

Autonomic Dysfunction

The autonomic nervous system is a major component of the endogenous defense mechanism to prevent hypotension. Autonomic dysfunction is prevalent in diabetes mellitus, paraproteinemias and other comorbidities associated with CKD and ESRD and blunts the sympathetic activation in response to intravascular volume reduction during HD. This results in impaired compensatory arteriolar vasoconstriction and increased risk of IDH.[43,44] Additionally, vascular calcification due to abnormal mineral metabolism is a common finding in patients on chronic dialysis.[45] The resultant arterial stiffness and associated endothelial dysfunction lead to insufficient vascular response to volume changes, increasing the risk of IDH.[46] Patients with vascular calcification and IDH are at higher risk for cardiovascular events.[47]

Splanchnic Blood Flow Shifts

Food ingestion during hemodialysis treatment transiently decreases blood volume in the large vessels and can cause splanchnic sequestration and vaso-relaxation, predisposing the patient to IDH.[48,49] This effect is less pronounced with high-protein meals, but more frequent in the presence of pre-existing autonomic dysfunction.[50,51]

Dialysate Temperature

Increased temperature of the external environment and/or the core temperature to 37°C or above during intermittent HD results in a reduction of peripheral vascular resistance. This can cause redistribution of blood volume to the vasodilated skin vessels and increases the risk of IDH.[52] Cooled dialysate below the patient's core temperature was shown to increase intradialytic MAP and to reduce the risk of IDH.[53]

Body Mass Index

Patients undergoing hemodialysis are susceptible to sarcopenia, which is associated with an elevated ratio of extracellular to intracellular water. While reporting is inconsistent, an association between body mass index (BMI) and IDH was postulated in patients with lower lean tissue index because skeletal muscle serves as a water reservoir with approximately 20% of this being dynamically mobile.[54,55] Other schools of thought propose the lean tissue index to fat tissue index ratio as a better indicator of IDH than BMI alone because obesity and sarcopenia are known to have a synergistic and negative impact on performance status.[56]

Antihypertensive Medication and IDH

The majority of ESRD patients on dialysis require the use of antihypertensive medications.[57] BP control is frequently complicated by IDH, especially when non-water-soluble drugs that are not cleared by HD are taken pre-HD. Nighttime dosing of these medications is being suggested to minimize the risk.[58] At the same time, use of antihypertensive drugs with negative chronotropic effects and alpha blockers are described to exacerbate IDH by impairing the compensatory responses.[59,60] These effects are more significant in the setting of acidosis due to suppressed cardiac contractility.[61]

Modality of Chronic Dialysis

Hemodiafiltration with large volume post-filter infusion of ultrapure fluid is predominantly practiced in Europe and the Far East and may have a potential to reduce IDH, though remains debated.[62,63] Part of the debate is centered around the possible cooling effect of post-filter infused fluid conferring the increased hemodynamic stability.[64] However, the evidence is questionable[65] and the technology is not uniformly available for all large dialysis provider chains, including not practiced in the United States. Moreover, on-line hemodiafiltration needs a somewhat different skill set for optimal patients management, which may not be intuitively immediately obvious.[66]

Accurate Measurement of Volume Status

Accurately assessing a patient's volume status is a crucial aspect of managing fluid balance in patients undergoing hemodialysis.[67] However, there is a lack of reliable and easily available methods for assessing ideal volume status, which presents a significant challenge for clinicians and researchers alike. Additionally, there can be a large disconnect between total body salt-water status and central filling pressures, further complicating clinical judgement. Several methods for assessing volume status have been developed, but each has its implicit limitations that need to be considered before clinical use. Bioimpedance spectroscopy is one such method that provides an accurate measurement of specific volume spaces, including extra and intracellular spaces.[68–70] However, this method can falsely suggest potentially removable fluid in error due to edemas mediated by low albumin states. Ultrasonographic assessment of lung B-lines is also helpful, but various technology platforms differ in accuracy and interpretation.[71,72] Blood volume monitoring has recently been incorporated into dialysis platforms, which affords the potential to predict capillary refill failure and potentially decrease dialysis-related morbid events in general.[73] One of the most promising methods for assessing volume status is the bedside assessment of central venous filling, including the inferior vena cava (IVC) and neck central veins.[74] Despite technological simplifications and increasing availability of ultrasound, none of these sonographic approaches are currently routinely used in outpatient dialysis practices. Excessive fluctuation of BP during dialysis may contribute to access thrombosis, further highlighting the importance of accurately assessing volume status to minimize complications.[75] Therefore, there is a need for further research to identify reliable and easily accessible methods for assessing ideal volume status in hemodialysis patients to improve clinical outcomes.

Consequence

Blood pressure fall during HD can be a stressful experience for patients and can significantly affect their quality of life and cognitive function.[76,77] This experience can result in an earlier termination of treatment, leading to inadequate volume and toxin removal.[78] Moreover, the frequency of IDH is associated with a longer dialysis recovery time.[79] IDH can cause end-organ ischemia, including myocardial stunning, and is associated with increased mortality.[10,21] Impaired tissue perfusion is more significant in the absence of vital organs auto-regulatory vasodilation, as seen in diabetic patients.[80] This is particularly relevant with higher UFR at thresholds of 10 or 13 mL/kg/h.[81] Furthermore, frequent IDH accelerates the loss of residual kidney function and increases mortality risk, as residual kidney function plays a significant role in fluid balance and toxin clearance, including bone mineral metabolites.[82] Additionally, IDH is also associated with vascular access thrombosis, a critical point of vulnerability for patients on HD, with considerable morbidity and additional costs associated with invasive procedures.[83] Therefore, managing and preventing IDH is crucial in improving the outcomes of patients on HD.

Prevention of IDH

Although the intermittent nature of HD treatments makes it less likely that IDH can be completely prevented, several strategies were described to decrease the frequency and severity of IDH, with the goal of reducing patient's stress and cardiovascular morbidity and mortality. Understanding the pathophysiology of IDH and using a modified and individualized dialysis prescription with or without pharmacological intervention are key components of this approach. Some of these strategies include:

1. Conducting a full assessment of cardiovascular status of at-risk patients, with or without significant cardiac history, to identify those who are most susceptible to IDH.[84]
2. Frequently and precisely assessing the patient's estimated dry weight (EDW) to avoid excessive fluid removal during HD.[85]
3. Restricting sodium in the diet to minimize interdialytic weight gain (IDWG) and the need for higher ultrafiltration rates (UFR).[86,87]
4. Avoidance of food intake during treatment to lower the frequency of IDH without compromising overall nutritional status.[88]
5. Adjusting sodium in the dialysate based on the patient's status to prevent significant IDWG as well as high UFR-associated IDH.[89]
6. Avoidance of high UFR of >10 mL/kg/hr in general.[90]
7. Conducting longer treatment sessions and slower reduction in plasma osmolality to mitigate hemodynamic instability.[29]
8. Avoiding low calcium in dialysate to prevent decreased left ventricular contractility.[91]
9. Reducing dialysate temperature, if tolerated, may prevent thermally induced reflex vasodilation.[92]
10. Using antihypertensive agents cautiously prior to dialysis based on pharmacodynamics.[93]
11. Using alpha-1 receptor agonist, midodrine, cautiously if there is no cardiovascular contraindication.[94]

Acute Treatment of IDH

Primary goal should be to address the patient's symptoms and discomfort while avoiding termination of treatment. This is crucial to ensure adequate clearance and prevent patients from leaving the dialysis unit volume overloaded or above their EDW. Several strategies can be employed to achieve this goal, including the following:

1. Stopping ultrafiltration: This can alleviate the decrease in intravascular volume and prevent further drop in BP during HD.
2. Placing the patient in Trendelenburg position: This can increase venous return and cardiac output, ultimately increasing BP.
3. Administering isotonic saline, if needed: This can help restore intravascular volume and prevent further hypotension.
4. Reassessing the prescription and UFR without terminating treatment: This can involve modifying the dialysis prescription to reduce the risk of IDH, such as reducing the target UFR or increasing the dialysate sodium concentration. It is important to note that any changes to the prescription should be done cautiously to prevent excessive ultrafiltration or electrolyte imbalances.

Research

The paucity of high-quality clinical trials limits strong recommendations for the prevention of IDH. The use of L-carnitine, a nutritional supplement that converts fatty acids to energy or online hemodiafiltration, as a convective blood purification technique to prevent IDH remain controversial strategies.[65,95,96] However, large trials that are increasingly unlikely to be funded in the era of shrinking resources limit the strong recommendation in prevention of IDH. More recently, machine-based learning methods now offer a fresh and potentially unbiased approach to tackling decades-old clinical problems. One large study reported that several variables, including pre-dialysis systolic BP, mean systolic BP during the previous HD session, UF target rate and IDH experience during the previous session were potentially predicting IDH.[97] Additionally, a Korean study demonstrated the efficacy of computer-derived deep learning in predicting IDH using data derived solely from the HD machine.[98] Further, a very recent paper described utilization of digitized EKG recording obtained within 48 h prior to dialysis session, to predict IDH.[99] Incorporating AI learning methods into dialysis supervision platforms could offer an advantage for the ongoing tasks of adjustment to and re-accommodation of local patterns and biases that impact care delivery. Thus, by leveraging machine-based learning methods, we can gain new insights into these clinical problems, leading to better prediction and prevention of complications during HD.

Conclusion

Despite numerous advances in dialysis management, IDH remains a pervasive problem. Due primarily to lack of a generally accepted definition, its true prevalence remains unclear. The clinical symptomatology of IDH broadly overlaps with effective intravascular volume depletion. It is associated with significant patient distress, recurrent episodes of transitory organ ischemia and an increased risk of immediate and future cardiovascular morbidity and mortality. A key pathological factor is the rapid fall in effective circulating volume with inadequate compensatory cardiovascular and neurohumoral response. Limiting weight gain between dialysis sessions, extending dialysis treatment time, reducing UFR and further individualizing HD prescription tailored to the patient's volume status could reduce both the frequency and severity of IDH. Implementing such interventions requires a multidisciplinary approach, including regular monitoring and timely adjustment of the HD prescription to optimize the patient's hemodynamic stability and a meaningful presence of nephrologists in the dialysis unit. The use of innovative technologies, such as machine-based learning, might aid in the detection and prediction of IDH, allowing for earlier interventions and improved patient outcomes.

Disclosure

Drs. Herberth and Fülöp are current employees of the United States Veterans Health Administration. However, the opinions and views expressed in this paper are the Authors' own and do not represent the official views or policies of the United States Veteran Health Administrations. Dr. Salem Vilayet is a current Fellow at the Department of Medicine - Division of Nephrology, Medical University of South Carolina (Class of 2024). The authors alone are responsible for the content and writing of the paper. The authors report no other conflicts of interest in this work.

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