특별강연 II

Management of Hemodynamic Instability in Hemodialysis Patients

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Intermittent hemodialysis induces rapid changes in fluid volume, body composition and osmolality status in chronic kidney disease patient. Intensity of these disorders is strongly dependent on the efficacy and the duration of the dialysis session. Rapid metabolic changes may lead to intradialytic symptoms, which vary, from minor discomfort (asymptomatic hypotension, fatigue, nausea, cramps…) to life threatening complications (collapse, shock, angina, arrhythmia, infarction, stroke).

Intradialytic symptomatology expresses dialysis maltolerance and is usually used as a surrogate marker of patient hemodynamic instability. Among these symptoms, the intradialytic hypotension is the most common clinical manifestation of unphysiological character of intermittent hemodialysis and a premonitory alarm for the imminent occurrence of a more severe clinical untoward event. Incidence of intradialytic hypotension is close to 20% but may vary in cohort studies from 6% to 27% of sessions. The definition of intradialytic hypotension is not universally defined or accepted. In the EBPG it is proposed to consider symptomatic intradialytic hypotension by coupling hypotension intensity with clinical manifestation (20 mmHg decrease in systolic BP systolic and 10 mmHg decrease of MAP). Frequent and/or severe intradialytic hypotensive episodes expose dialysis patient to recurrent ischemic insults (cardiac, cerebral and intestinal) and increase relative risk of cardiovascular mortality.

Intradialytic hypotension results from the interplay of five major factors of dialysis prescription: 1. Ultrafiltration rate; 2. Volemia preservation; 3. Cardiovascular reactivity; 4. Hemodialysis modality and thermal balance; 5. Electrolyte dialysate composition.

Hemodynamic instability is clearly more frequently observed in elderly, female subject and comorbid patients (diabetics, cardiac, malnourished or inflamed). That needs to be worked out when all current usual manouvers described below have failed.

Management of hemodynamic instability in hemodialysis patient described in this presentation relies on this basic mechanistic consideration and on a stepwise approach. Hemodialysis prescription is a crucial step in the customization of the renal replacement therapy to improve its cardiovascular and overall tolerance. Thus, it is under the physician's responsibility to identify the best therapeutic options based on a patient specific probing approach.

1. Ultrafiltration rate is a major determinant of blood volume preservation in intermittent hemodialysis. Several studies have confirmed a clear relation between symptomatic hypotension and the ultrafiltration rate or the total amount of fluid removed. When ultrafiltration rate exceeds vascular refilling rate from venous and interstitial compartments the blood volume starts to decline progressively. The degree to which blood volume declines during a constant ultrafiltration rate differs between patients and depends on several factors (extracellular fluid overload, oncotic pressure, cardiovascular adaptation, hemodialysis modalities and electrolyte prescription …). Ultrafiltration rate and total ultrafiltration (i.e. weight loss per session) depends on fluid status of the patient and the necessity to correct fluid overload accumulated during the interdialytic period. In clinical practice, fluid management relies mainly on probing patient "dry weight". Dry weight is a clinical concept that corresponds to an ideal situation in which homeostasis of fluid balance of chronic kidney disease patient has been restored by hemodialysis. Dry

weight is commonly defined as the weight below which the patient is free of edema, normotensive without symptomatic complaints during and after dialysis. However, this clinically-driven strategy may fail to assess the optimal fluid status of the patient and more objective methods (e.g., biomarkers, bioimpedence and imaging methods) are clearly needed, since on one hand chronic fluid overload is known to be deleterious for the cardiovascular system of the patient (atherosclerosis, left ventricular hypertrophy or dilatation) but on the other hand, hypovolemic state has been implicated in severe ischemic organ damage (cardiac stunning, cerebral leukoaraiosis, gut ischemia and endotoxin translocation). Several studies have now established that the safe range of ultrafiltration rate is close to 10 ml/h/kg (700-800 ml/h) while overpassing 13 ml/h/kg exposes the patient to cardiovascular events and increases mortality risk. Accordingly, all dialysis prescription schedules should comply with this quite simple measure either by extending treatment time, or adding extra ultrafiltration sessions, and reducing salt intake by diet counseling.

2. Volemia preservation is a critical point that should be kept in mind as a priority for dialysis patient. During hemodialysis, fluid is removed from the intravascular space by ultrafiltration while applying a hydrostatic pressure gradient between blood and dialysate compartment. Sodium depletion during hemodialysis is achieved mainly by ultrafiltration (80-90%) and to a minor extent by diffusion (10-20%) depending on the sodium gradient between blood and dialysate compartment. Ultrafiltration is usually combined to hemodialysis (weight loss) or may be performed sequentially (isolated ultrafiltration) without concomitant hemodialysis treatment for cardiovascular reason. As a result of ultrafiltration, decrease of the intravascular pressure and increase in the colloid osmotic pressure tends to facilitate fluid shift from interstitial space to vascular compartment, which partly compensates for the fluid removed. However, in most cases, vascular refill will not be complete and blood volume will decrease. In particular, higher ultrafiltration rate are more likely to be associated with a larger decrease of intravascular volume and then prone to induce hypotension. Several mechanisms, mainly related to the dialysis treatment prescription but also patient related factors, will influence blood volume preservation and therefore hemodynamic stability. A decrease in blood volume up to 20% may be tolerated in healthy or fluid overload subjects, whereas in elderly, comorbid patients (cardiac, diabetic, and autonomous neuropathic…) or hypovolemic patients, hypotension may occur with much less reduction in blood volume. The tolerance of sodium and fluid depletion may differ from patient to patient, from treatment to treatment and from time to time. In order to preserve volemia and prevent further additional cardiovascular insults, it is strongly recommended to monitor blood volume changes during hemodialysis session and customize ultrafiltration rate to vascular refilling rate individually.
3. Cardiovascular reactivity is an essential component to compensate for blood volume reduction in hemodialysis patient and prevent hypotension. Major determinants of hemodynamic adaptation facing acute hypovolemia include an increase in cardiac output (increase of heart rate, sympathetic activity increase and myocardial contractility), a rapid and effective volume mobilization (venous return increase) and an increase in peripheral vascular resistance. Responses of heart and vascular reactivity to acute hypovolemia are clearly dependent on cardiovascular status and sympathetic pathways of the dialysis patient. However, these factors may be to some extent modulated by dialysis prescription such as dialysis modality, treatment schedule, dialysate electrolyte composition, thermal balance and use of specific medications.
4. Hemodialysis modality and thermal balance have been shown to play an important role in hemodynamic stability of hemodialysis patients. The hemodialysis treatment per se appears to be primarily responsible for the impaired vascular response to acute hypovolemia. Isolated ultrafiltration (UF) preserves better vasoconstrictor responses to hypovolemia. In contrast to conventional hemodialysis, convective modalities (hemofiltration, HF and hemodiafiltration, HDF) have been shown to better preserve vasoreactivity and hemodynamic response to hypovolemia and to reduce significantly symptomatic hypotension episodes. Initially, hemodynamic superiority of convective mo-

dalities was associated either with release of vasoconstrictive peptides (catecholamines, vasopressin, renin, endothelin), or linked to a discrete positive sodium mass balance (online fluid substitution) and/or to the removal of vasodilator peptides (NO). Nowadays, clinical benefit of convective therapies is linked essentially to the negative thermal balance provided by these modalities. Indeed, several clinical studies have confirmed that by matching thermal balance, conventional hemodialysis achieves almost the same level of hemodynamic stability than convective modality. Based on these clinical findings, it is now strongly recommended to ensure an isothermic session on a regular basis (no energy gain) and proposed a slightly cooling dialysis (negative energy gain) for hypotensive prone patients.

5. Electrolyte dialysate composition is also a crucial component for preserving hemodynamic stability during hemodialysis session. Dialysate sodium concentration plays a major role in hemodynamic stability and tolerance of hemodialysis. Due to its dual activity dialysate sodium influences net sodium mass transfer and exerts a determinant role on osmolality changes and brain variations. On one hand, dialysate sodium and dialysate–patient gradient affects sodium and water fluxes between patient and dialysate and contributes to volemia preservation (e.g., low dialysate sodium enhances patient–dialysate diffusive sodium flux and reduces volemia, while high dialysate sodium reduces patient–dialysate diffusive sodium flux and tends to increase volemia). Although diffusive sodium flux represents a minor part of sodium mass transfer, compared to ultrafiltration rate, it may affect significantly volemia changes and tolerance. On the other hand, dialysate sodium concentration counterbalances for osmotic changes and contributes to improve dialysis tolerance: high dialysate sodium (>plasma sodium concentration) facilitates vascular refilling, reduces effects of osmotic changes due to rapid osmotically active solute removal (disequilibrium syndrome) but exposes patient to chronic sodium gain; low dialysate sodium (<plasma sodium concentration) compromises vascular refilling capacity and enhances hemodialysis intolerance faced to rapid solute removal. In the earlier days, low dialysate sodium was commonly used to ensure extracellular volume correction and blood pressure control. Nowadays, this approach is rarely applied in short treatment program since it is associated with an increased incidence of hypotensive episodes and an overall maltolerance of dialysis sessions.

The dialysis fluid buffer also influences blood volume preservation and hemodynamic stability. Bicarbonate buffer is a new standard universally accepted since associated with better hemodynamic stability and dialysis tolerance. However, the low acetate concentration sill present in acid dialysis concentrate is putatively associated with side effects in compromised patients (cardiac, elderly, malnourished, low weight) being potentially involved in further impairment of refill blood volume capacities and cardiodepressant effects. Several recent clinical studies indicate that substituting acetic acid by chloric acid or better citric acid may further improve hemodynamic stability of hemodialysis sessions.

Dialysate calcium and magnesium concentrations contribute to hemodynamic stability in hemodialysis patient. Low calcium (<1.25 mM/L) and low magnesium (<0.25 mM/L) concentrations are clearly not recommended since enhancing hemodynamic instability in compromised patients. In addition, dialysis fluid buffer composition and potassium concentration should be considered when prescribing dialysate calcium and magnesium. Citrate–based dialysate complexes calcium and magnesium and require a 25% higher concentration of these cations. Low dialysate potassium (< 3 mM/L) is not recommended in conjunction with low dialysate calcium and magnesium increasing risk of severe arrhythmia and hemodynamic instability.

Advanced age, female gender and comorbid condition (cardiomyopathy, cardiac impairment, arrhythmia, autonomic neuropathy, severe anemia, iron deficiency, medications, vitamin B or carnitine deficiency…) are critical components that potentiate intradialytic hypotension and hemodynamic instability in hemodialysis. Following a checklist approach, more specific and organic cause needs to be worked up when current maneuvers have failed. A list of the main related causes is provided in Table 1.

Conclusion

Hemodynamic instability is relatively common in hemodialysis and reflects unphysiology of intermittent renal replacement therapy. It is directly linked to the large fluid removal and electrolytic and metabolic changes that occur simultaneously during hemodialysis sessions. In this context, long nocturnal of dialysis sessions and/or more frequent sessions have been shown to reduce hemodynamic instability.

Nowadays, recognizing that short treatment schedules are the most commonly accepted modalities for personal convenience or cost-effectiveness reasons, one must compromise with this challenge.

A pragmatic approach based on dialysis prescription and best use of currently available tools will be discussed in this presentation, in order to reduce hemodynamic instability and improve outcomes of hemodialysis patients. Stepwise approach acting on the five major components of dialysis prescription (ultrafiltration rate; volemia; cardiovascular reactivity; hemodialysis modality and thermal balance; electrolyte dialysate composition) interplaying on the occurrence of hypotensive episodes is proposed. Now, it also implicitly recognized that hemodynamic instability might be linked to cardiovascular compromised profile of dialysis patients. That needs to be worked out when all usual maneuvers described fail to improve the clinical situation.

Table 1.

Normal adaptation to hypovolemia hemodialysis-induced :

- Maintenance of cardiac output = increase in heart rate and myocardial contractility
- Increase in peripheral vascular resistance =constriction of resistance vessels
- Constriction of capacitance vessels

Inadequate adaptation to hypovolemia hemodialysis-induced :

1. Patient-related factors:

Cardiac factors (decrease cardiac output)
  Cardiac disease: systolic (LVH) or diastolic dysfunction
  Cardiac failure
  Cardiac arrhythmias
Vascular resistance and capacitance vessels (impairment of vascular resistance)
  Decrease arteriolar constriction
Vein and veinule tone (impairment of venous return)
  Reduction in venoconstriction (centralize blood volume)
Autonomic neuropathy:
  Impairment of sympathetic/parasympathetic (vagal tone) (e.g., diabetic)
Bradycardic Bezold-Jarish reflex (secondary to ventricular underfilling)
  Medications (beta blocker)
Other factors
  Arteriopathy,
  Anemia,
  Iron deficiency,
  Functional hypovolemia (digestion, post prandial, hypoglycemia…)
  Nutritional or vitamin or micronutrient deficiencies

2. Treatment time and dialysis strategy:

Short treatment time (<3 hours)
High ultrafiltration rate (>10 ml/hr/kg)
Uncompliant patient (important interdialytic weight gain)
Fluid overload patient

3. Dialysis-related factors:

Electrolytic dialysate composition
  Dialysate buffer (acetate, increased production of nitric oxide)
  Dialysate calcium and magnesium concentrations (low concentrations)
  Dialysate sodium concentration (low sodium)
Dialysate purity and material biocompatibility
  Induction of cytokines (contaminated dialysate)
  Bioincompatibility of dialysis membrane
Dialysis thermal balance (increase in core temperature)