Nephrol Dial Transplant (2007) 22 [Suppl 2]: ii22–ii44
doi:10.1093/ndt/gfm019

NDT
Nephrology Dialysis Transplantation

EBPG guideline on haemodynamic instability

Jeroen Kooman[1], Ali Basci[2], Francesco Pizzarelli[3], Bernard Canaud[4], Patrick Haage[5], Denis Fouque[6], Klaus Konner[7], Alejandro Martin-Malo[8], Luciano Pedrini[9], James Tattersall[10], Jan Tordoir[11], Marianne Vennegoor[12], Christoph Wanner[13], Piet ter Wee[14] and Raymond Vanholder[15]

[1]Department of Internal Medicine, division of Nephrology, University Hospital Maastricht, The Netherlands, [2]Department of Medicine; division of Nephrology, Ege University Medical Faculty, Izmir, Turkey, [3]Nephrology Unit, SM Annunziata Hospital, Florence, Italy, [4]Nephrology, Dialysis and Intensive Care Unit, Lapeyronie University Hospital, Montpellier, France, [5]Department of Diagnostic and Interventional Radiology, Helios Klinikum Wuppertal, University Hospital Witten/Herdecke, Germany, [6]Département de Néphrologie JE 2411-Dénutrition des Maladies Chroniques, Hôpital E Herriot, France, [7]Medical Faculty University of Cologne, Medicine Clinic I, Hospital Merheim, Germany (retired), [8]Nephrology Department, Reina Sofia University Hospital, Cordoba, Spain, [9]Division of Nephrology and Dialysis, Bolognini Hospital, Seriate, Italy, [10]Department of Renal Medicine, St. James's University Hospital, Leeds, UK, [11]Department of Surgery, University Hospital Maastricht, The Netherlands, [12]Department of Nephrology, Nutrition and Dietetics, Guy's and St Thomas' NHS Foundation Trust, London, UK (retired), [13]Department of Medicine, Division of Nephrology, University Hospital, Würzburg, Germany, [14]Department of Nephrology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands and [15]Nephrology Section, Department of Internal Medicine, University Hospital, Ghent, Belgium

Outline

Correspondence and offprint requests to: Jeroen P. Kooman, MD, PhD, Department of Internal Medicine, Division of Nephrology, University Hospital Maastricht, PO Box 5800 6202 AZ Maastricht, The Netherlands. Email: jkoo@sint.azm.nl

Keywords: dialysis; guideline; haemodynamic; hypotension; instability

Introduction

Definition of intra-dialytic hypotension

In the literature, the definition of intra-dialytic hypotension (IDH) is not standardized and differs between various studies. Most definitions however, take into account either a relative or an absolute decline in blood pressure (BP) as well as the presence of specific symptoms. Although no evidence based recommendation regarding the definition of IDH can be given, the EBPG working group stresses that both a reduction in BP, as well as clinical symptoms with need for nursing intervention should be present in order to accept the presence of IDH. Moreover, the definition of IDH should ideally be equal in the literature and different treatment guidelines. Conforming to the K/DOQI guidelines, a proposed definition is a decrease in systolic BP $\geq$20 mmHg or a decrease in mean arterial pressure (MAP) by 10 mmHg associated with clinical events and need for nursing interventions.

Incidence of IDH

In reviews, a 20% incidence of intra-dialytic hypotension is widely cited [1,2]. The reported incidence in cohort studies varies between 6% and 27% [3,4]. In the largest cohort reported so far, 10% of patients had frequent hypotensive episodes whereas 13% occasionally had hypotensive episodes [5]. The sensitivity for IDH may also vary among individual patients [6].

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Relation between IDH and outcome

In review papers, IDH has been given a putative causal role in myocardial and cerebral ischaemia. A recent study, found significant increases in creatine kinase MB levels at the end of HD therapy and in circulating troponin I levels 44 h following HD after an episode of IDH, in contrast to uneventful treatments [1]. IDH was an independent and negative predictor of long-term fistula outcome [2]. In a longitudinal study, frequent episodes of IDH were found to be related to frontal lobe atrophy [3]. In a cohort of 20 patients with non-occlusive mesenteric ischaemia, all episodes were preceded by IDH [4].

In a case-control study, a relation between IDH and 2-year mortality was observed, which lost significance after correction for confounding factors [5]. In a prospective cohort study of 1244 patients, an independent relationship between IDH and 2-year mortality was observed [6]. However, this study did not include cardiac disease as a potential confounding factor.

Therefore, it remains unknown whether IDH plays a causative role in adverse outcome or is merely a marker of comorbid conditions, which increase the sensitivity for IDH.

IDH may also impair solute clearance, due to compartmentalization of blood volume [7] and premature termination of dialysis sessions.

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Patients at risk for IDH

Few large scale studies have addressed potential risk factors for IDH. The largest multi-centre cohort

study was reported by Tisler *et al.* [1]. Of a cohort of 958 patients from 11 dialysis centres, 96 patients with frequent episodes of IDH were compared with 130 patients with occasional episodes of IDH. Age, female sex, presence of diabetes mellitus, hyperphosphataemia, presence of coronary artery disease, and renal diagnosis other than glomerulonephritis and the use of nitrates were significantly higher in patients with frequent IDH. In multivariate analysis, age, renal diagnosis other than glomerulonephritis, hyperphosphataemia and the use of nitrates were independent risk factors for IDH. In another study, hypotensive episodes occurred frequently in 44% of dialysis patients of ≥65 years and in 32% of younger dialysis patients (age <45 years) [2]. One study also found lower albumin levels in patients with hypotension during haemodialysis [3].

Cardiac abnormalities may increase the risk for IDH. In an observational study in 15 dialysis patients, the decline in BP was larger in patients with systolic dysfunction, compared with patients with normal systolic function [4]. Also, diastolic dysfunction may increase the risk for IDH. In an observational study with 47 haemodialysis patients, those with frequent IDH episodes had more severe concentric left ventricular hypertrophy, lower pre-dialysis BP and impaired diastolic left ventricular filling [5]. Although it is often considered that anaemia is a risk factor for IDH, especially in patients with cardiac disease, there has been no study addressing this relationship.

Also, the existence of autonomous neuropathy was found to be a risk factor for IDH in most [6–11], but not all studies [12,13].

The sensitivity of patients for IDH may not be a stable condition. Seven patients who frequently experienced IDH episodes were found to have large differences in the incidence of IDH over a 24-month period [14]. Moreover, there are seasonal variations in BP behaviour among chronic HD patients [15].

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Pathophysiology of IDH

During haemodialysis combined with ultrafiltration, a decline in circulating blood volume usually occurs, depending upon the ultrafiltration rate and the degree of refill of blood volume from the interstitial compartment. Refill of blood volume depends upon various factors, such as the hydration state of the interstitial compartment, dialysate sodium concentration, capillary permeability, venous compliance and protein balance [1,2]. Accordingly, plasma refilling rate is patient-specific, and the ensuing variations in BV show a large intra-individual as well as inter-individual variability [3,4]. Under physiological circumstances, a decline in blood volume initially leads to an increase in peripheral vascular resistance, due to constriction of resistance vessels, maintenance of cardiac output, due to an increase in heart rate and myocardial contractility, and constriction of capacitance vessels [2,5]. Healthy persons can tolerate a decline in circulating blood volume up to 20% before hypotension occurs [6,7]. However, in dialysis patients, hypotension may occur with a much smaller decline in blood volume [8].

In patients prone to hypotension, the critical blood volume decline at which IDH occurred shows large inter-individual [from 2% to 29%], but also a large intra-individual variation [8,9]. Several mechanisms may be responsible for this phenomenon. First, the normal cardiac response to hypovolaemia, consisting of an increase in heart rate and myocardial contractility, may be impaired. It has been shown that the presence of cardiac disease, leading to systolic or diastolic dysfunction, increases the risk for IDH. At comparable ultrafiltration rates, the decline in BP was larger in patients with systolic dysfunction, compared with patients with normal systolic function [10,11], whereas in patients prone to IDH, left ventricular hypertrophy was more severe and diastolic filling was impaired [10,12]. Although it is likely that cardiac arrhytmias may increase the sensitivity of the patient for IDH, no literature on this subject is available.

Factors related to the dialysis treatment, such as the dialysate buffer and calcium concentration, may influence cardiac contractility [12,13]. In the absence of cardiac disease, no difference in myocardial contractility was observed among patients, with or without frequent episodes of IDH [14].

The presence of autonomic neuropathy, which can be assessed using standardized function tests or spectral analysis of heart variability, may impair the heart rate response during hypovolaemia, although in non-diabetic patients its role in the pathogenesis of IDH remains controversial [15–20]. A bradycardic, so called Bezold-Jarish reflex has also been observed during IDH episodes. This reflex is believed to result from sudden sympathetic withdrawal due to severe ventricular underfilling [5,21,22]. Several papers showed an impairment of sympathetic function, as shown by a reduction in the low frequency heart rate variation and low and high frequency ratio by spectral analysis, in unstable dialysis patients [23,24]. Apart from cardiac factors, the normal reaction of the resistance and capacitance vessels during a decline in blood volume may be impaired during dialysis treatment [25]. A decreased arteriolar constriction may compromise the physiological increase in systemic vascular resistance during hypovolaemia. A reduction in the passive and active constriction of venules and veins, which serve to centralize blood volume during hypovolaemia, impairs venous return [5,26–29].

Various explanations for the reduced reactivity of resistance and capacitance vessels have been proposed, such as induction of cytokines, bioincompatibility of the dialysis membrane, the use of acetate as dialysate buffer, an increased production of nitric oxide or an insufficient increase in vasoconstrictors such as vasopressin during fluid removal [30–34]. Thermal effects appear to be of great importance in the inadequate vascular response during haemodialysis. Haemodialysis induces an increase in core temperature, even when no additional energy is transferred from the extracorporeal circuit to the patient. The increase in core temperature antagonizes the normal vascular response to hypovolaemia [35–37].

In conclusion, IDH may occur as a result of a decline in blood volume, impaired cardiac response and impaired constriction of resistance and capacitance vessels. Depending on patient- and treatment-related factors, the relative importance of these factors may vary.

Strategies for prevention and therapy of IDH are based upon influencing one or more of these pathogenetic factors.

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Prevention of IDH

1. Evaluation of the patient

Rationale

- **Guideline 1.1.1 Hydration state should be regularly assessed by clinical examination (Opinion).**
- **Guideline 1.1.2 Objective methods to assess fluid state should be considered in a patient with frequent IDH when clinical examination is inconclusive (Level III).**

Incorrect assessment of dry body weight may result either in underhydration or overhydration in dialysis patients. Earlier studies have shown that a significant percentage of unstable patients were normohydrated or underhydrated at the start, and very frequently underhydrated at the end of the dialysis session [1,2].

In underhydrated patients, the interstitial volume is restricted and refill to blood volume is hampered, resulting in a larger decline in blood volume for a given ultrafiltration rate [3]. On the other hand, overestimation of dry body weight may result in hypertension and put the patient at risk for cardiac dilatation and pulmonary oedema.

Physical examination should always be the basis for assessment dry weight in dialysis patients. However, as sometimes physical examination allows no definite conclusion [4], several non-invasive methods have been developed. Cardiothoracic ratio by X-ray is able to detect overhydration [5,6], but has not been formally tested as a tool for the prevention of IDH.

Inferior caval vein diameter, assessed by echography, correlated with blood volume and right atrial pressure and predicted haemodynamic changes during dialysis. Multifrequency bioimpedance analysis was able to predict haemodynamic instability in some [7,8], but not all [9] studies. Bioimpedance analysis is also very sensitive in detecting changes in fluid state [10,11–13]. With the vector bioimpedance method, reactance and resistance measurements are obtained from single frequency bioimpedance measurements. Reference tolerance ellipses, derived from a healthy population, are applied. With the vector bioimpedance method, it was possible to differentiate hypotensive-prone from stable patients [13]. Also thoracic impedance measurements have been used to predict IDH, but evidence is still limited [14].

The biochemical marker cGMP, but not ANP, predicted haemodynamic changes during dialysis

[8,15]. Both cGMP and ANP are released in response to left atrial stretch. However, whereas cGMP was found to be potentially useful in the diagnosis of overhydration, it was not able to predict underhydration [8,15]. Also brain natriuretic peptide, released in response to left ventricular stretch, predicted overhydration, but not underhydration [16].

It has been postulated that a patient-specific individual decline in blood volume exists, below which the patient is at risk for hypotension [17]. One study showed a patient-specific decline in blood volume with a standard deviation <5% in the majority (75%) of patients [18]. However, other studies did not find assessment of BV changes during dialysis to be of use in the prediction of IDH [19,20].

A major issue with the use of objective techniques is the definition of appropriate cut-off values. Although normal values for inferior caval vein diameter (IVCD) have been proposed [8], the timing of measurements is of pivotal importance [21]. For IVCD, Chang *et al*. [22] applied a reference value of 8 mm/m^2 obtained 2 h after dialysis. Reference values for bioimpedance techniques may be population specific [23,24], although the use of vector bioimpedance [10] might circumvent this problem.

Few studies assessed whether the use of objective techniques is able to reduce the incidence of IDH. In one randomized controlled trial by Chang including 100 patients, the use of vena cava echography resulted in a reduction of IDH, compared with patients in whom dry weight was assessed on clinical grounds. Moreover, quality of life was improved [22,25]. In another study, the same group showed beneficial effects of dry weight assessment by IVCD on cardiac structure [26]. Nevertheless, vena cava echography is operator dependent and may be less reliable in patients with cardiac disease and especially tricuspid insufficiency [21] or pericardial effusion. Moreover, measurements may be difficult to interpret in obese patients and patients with polycystic kidney disease [27]. Under research conditions, inter- and intra-observer variability for IVCD measurement were <5 and 2.5% [27].

Summarizing, although several objective methods were able to predict changes in BP and other haemodynamic parameters during dialysis or the occurrence of IDH, at present only the use of vena cava echography has been shown to result in a reduction of IDH. However, this technique is also operator dependent and may be difficult to interpret in patients with cardiac failure. Moreover, the timing of measurement should be standardized. Although the use of bioimpedance has not yet been shown to result in a reduction of IDH, this technique might be useful to detect changes in hydration state.

Recommendations for research

To establish cut-off values for bioimpedance measurements; to investigate the effect of dry weight prescription based on bioimpedance measurements on IDH.

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- **Guideline 1.2 Blood pressure and heart frequency rate should be measured frequently during dialysis in order to anticipate IDH (Opinion).**

Rationale

Two types of hypotensive episodes have been distinguished during dialysis (bradycardic and tachycardic). Most frequently, episodes of IDH are preceded by a gradual decline in BP and increase in heart rate [1]. Alternatively, IDH episodes may occur suddenly and be associated with a bradycardic response (Bezold Jarish reflex), which is believed to originate from activation of left ventricular mechanoreceptors due to severe ventricular underfilling [2–5]. In the tachycardic type of IDH, it is conceivable that IDH may be prevented by adjusting ultrafiltration, although no studies have been performed into this subject.

Recommendations for research

To compare clinical monitoring vs device-assisted monitoring in predicting IDH.

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- **Guideline 1.3 Cardiac evaluation should be performed in patients with frequent episodes of IDH (Opinion).**

Rationale

It has been shown that the presence of cardiac disease, leading to systolic or diastolic dysfunction of the heart increases the risk for IDH. An increase in myocardial contractility is a physiological response to a decline in blood volume, which can be impaired by systolic dysfunction of the heart. During comparable ultrafiltration rates, the decline in BP was larger in patients with systolic dysfunction compared with patients with normal systolic function [1]. Diastolic dysfunction increases the sensitivity of the patient for changes in preload, i.e. both for under- and overhydration. In patients prone to IDH, diastolic filling was found to be impaired [1,2]. A potential problem with the assessment of diastolic dysfunction in haemodialysis patients is the fact that indices which are used to assess diastolic dysfunction are preload dependent [3]. Diastolic dysfunction is often related to the presence of left ventricular hypertrophy, but may also be due to myocardial ischaemia or fibrosis [4]. The presence of supraventricular arrhytmias may also compromise ventricular filling, which may be especially evident in patients with systolic or diastolic dysfunction [2]. Echocardiography is a simple and non-invasive tool and was, therefore, considered by the EBPG working group as a useful tool to initiate cardiac evaluation. Based on the echocardiographic findings and the clinical assessment of the patient, further cardiologic evaluation of the patient may be warranted. The working group recognizes, however, that this guideline is opinion based, as no study yet assessed

the effect of cardiac evaluation on the prevention of IDH.

Summarizing, systolic and diastolic function of the heart increases the risk for IDH. No study assessed the effect of echocardiographic evaluation as a tool to modify treatment in order to prevent IDH. Echocardiographic parameters to assess diastolic dysfunction are preload dependent.

Recommendation for research

To establish preload independent markers for diastolic dysfunction. To investigate the role of echocardiography as a tool to modify treatment to prevent IDH.

References

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2. Lifestyle interventions

- **Guideline 2.1 In order to control inter-dialytic weight gain and reduce the risk of IDH, dietary salt intake should be assessed and not exceed 6 g/day unless contra-indicated (Evidence level III).**

Rationale

A large inter-dialytic weight gain may increase the sensitivity for IDH because ultrafiltration rate has to be increased if dialysis time is not adjusted, leading to a larger decline in blood volume. Although other factors, such as xerostomia, may be involved in thirst in dialysis patients [1], osmotic thirst due to insufficient attention for salt restriction also appears to play a major role in increasing inter-dialytic weight gain in dialysis patients [2]. Salt restriction decreases inter-dialytic weight gain and improves inter-dialytic BP control [3]. Two non-randomized cross-over studies assessed the effect of salt restriction on inter-dialytic weight gain and incidence of IDH. Interdialytic weight gain decreased significantly with salt restriction, as did the decline in relative blood volume, and incidence per session of IDH: 0.71 ± 0.8 (usual sodium intake) *vs* 0.18 ± 0.5 (salt restriction) [4]. In the other study, the monthly incidence of IDH episodes decreased from 22% to 7% after strict sodium restriction [5]. Except in patients with obligatory sodium loss, such as salt-loosing nephritis, sodium restriction is thus indicated in dialysis patients to reduce inter-dialytic weight gain.

In diabetic patients, hyperglycaemia may stimulate thirst and thus inter-dialytic weight gain [2,6], suggesting that strict glucose control might reduce inter-dialytic weight gain. However, no data on the relation between glucose control and inter-dialytic weight gain in dialysis patients are yet available.

Summarizing, reducing salt intake (2 g/90 mmol Na or 6 g NaCl) can reduce inter-dialytic weight gain and may play a role in the prevention of IDH.

Recommendations for research

To study the role of drugs which may reduce salt appetite (e.g. ACE inhibitors).

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- **Guideline 2.2 Food intake during or just before dialysis should be avoided in patients with frequent episodes of IDH (Evidence level II). In malnourished patients, the haemodynamic effects of food intake during dialysis should be balanced against the nutritional needs of the patient (Opinion).**

Rationale

Food intake during dialysis may lead to splanchnic vasodilation and thus contribute to IDH [1]. Three studies, two randomized cross-over and one non-randomized cross-over study, showed a larger decline in BP and a higher incidence of IDH after food intake [2–4]. Caffeine did not appear to have a preventive effect on IDH [4]. No study has yet assessed the effect of meals taking just before dialysis treatment on IDH. However, it is likely that the haemodynamic effect

will be comparable. In malnourished patients, the haemodynamic effects of food intake during dialysis should be balanced against the nutritional needs of the patient.

Summarizing, food intake during dialysis increases the sensitivity for IDH, whereas caffeine does not seem to have a preventive effect.

Recommendations for research

Assess the haemodynamic effects of meals (light or heavy) before dialysis treatment.

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3. Factors related to the dialysis treatment

3.1 Optimizing ultrafiltration: ultrafiltration profiling and blood volume controlled ultrafiltration

- **Guideline 3.1.1 Pulsed ultrafiltration profiles should not be used for the prevention of IDH (Evidence level III).**

Rationale

By ultrafiltration profiling, the change in blood volume can be influenced. The most commonly used ultrafiltration profiles are characterized by an initially high ultrafiltration rate, followed by a linear decrease in ultrafiltration rate, or intermittent ultrafiltration pulses followed by periods of minimal ultrafiltration. Most ultrafiltration profiles have been studied in combination with sodium profiles and are discussed separately. One cross-over study with 53 patients found a reduced incidence of IDH during linear ultrafiltration, whereas pulsed profiles resulted in an increase in IDH [1]. In contrast, a randomized cross-over study in 12 patients [2] showed an increased incidence of IDH with a linear decreasing ultrafiltration profile. In two randomized cross-over studies, no difference in IDH was observed between treatments with ultrafiltration profiling without sodium modelling and constant ultrafiltration [3,4].

Due to conflicting evidence, no conclusions can be made regarding the use of linear decreasing ultrafiltration profiles for the prevention of IDH.

Summarizing, evidence for the effectiveness of ultrafiltration profiling is conflicting. Pulsed profiles may result in an increase in IDH.

Recommendations for research

To perform larger randomized studies to the effect of linear decreasing ultrafiltration profiling on IDH.

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- **Guideline 3.1.2a Individualized, automatic BV control should be considered as a second-line option in patients with refractory IDH (Evidence level II).**

- **Guideline 3.1.2b Manual adjustment of ultrafiltration according to a fixed protocol based on changes in blood volume should not be performed (Evidence level II).**

Rationale

With blood volume controlled treatments, ultrafiltration rate and/or dialysate conductivity are adjusted according to changes in relative blood volume. This can either be performed automatically by a feedback module in the dialysis machine, which adjusts ultrafiltration and/or dialysate conductivity when the changes in relative blood volume deviate from a preset curve [1,2], or can be performed manually in response to measured on-line changes in blood volume [3]. It is thus possible to prevent the decline in blood volume beyond the point at which the patient is presumed to be at risk for IDH. The existence of a patient specific critical decline in blood volume remains controversial, however (see pathophysiology of IDH). Nevertheless, several randomized cross-over studies have shown a reduction in IDH and intra-dialytic symptomatology with the use of automatic blood volume controlled feedback [1,2,4–6]. Moreover, one study showed an increase in dialysis efficacy with the use of this approach, due to a reduction in

intra-dialytic interventions [1]. Automatic blood volume controlled feedback options are available only on a limited number of dialysis modules. Most studies used the feedback approach in which both ultrafiltration rate and dialysate conductivity are modelled, and in which the mean dialysate conductivity was usually set at 14.0 mS/cm. No adverse effects on sodium balance have yet been reported [2,7]. No comparison with other strategies has been performed.

Regarding manual adjustment of ultrafiltration according to blood volume changes, a multi-centre randomized study that included 443 patients has been performed. In this study, adjustment of ultrafiltration was based on a fixed, non-individualized protocol. In comparison to conventional monitoring, no benefits of blood volume controlled treatments on IDH were observed, whereas an increase in mortality and hospitalization was observed. The authors of this study could provide no definite explanation for these findings [3]. However, mortality in the control group was less than that observed in the prevalent dialysis population.

It is not clear whether the results of this study can be extrapolated to automatic blood volume control, based on individualized blood volume targets. Given the fact that the effect of automatic blood volume feedback control on mortality has not yet been assessed, the EBPG working group felt that, despite demonstrated benefit on IDH, no definite recommendation for the application of automatic blood volume control as a first-line option can be made. However, if available, automatic BV controlled feedback can be attempted as a second-line option in patients with refractory IDH.

Summarizing, various studies have shown a beneficial effect of automatic blood volume controlled feedback in the prevention of IDH episodes. However, an increase in mortality was observed with manual adjustment of ultrafiltration according to BV changes.

Recommendation for research

To investigate the effects of automatic blood volume control on mortality.

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3.2 Dialysate composition

3.2.1 Dialysate sodium

- **Guideline 3.2.1 Although sodium profiling with supraphysiological dialysate sodium concentrations and high sodium dialysate (≥144 mmol/l) are effective in reducing IDH, they should not be used routinely because of an enhanced risk of thirst, hypertension and increased inter-dialytic weight gain (Evidence level II).**

Rationale

Dialysate sodium plays an important role in the refill of blood volume from the interstitial compartments. Refill of blood volume from the interstitial to the intravascular compartment will be low if interstitial hydration is low [1]. With high dialysate sodium concentrations, fluid shifts from the intracellular compartments are enhanced, whereas with low dialysate sodium concentrations, disequilibrium between the intra- and extracellular compartments may occur. Thus, with low sodium dialysis, refill of blood volume from the interstitial compartments will be impaired because of the shift of fluid from the interstitial to the intracellular compartments, whereas with supraphysiological sodium concentrations of the dialysate, fluid will shift from the intracellular to the interstitial compartments, which will in turn enhance the refill of blood volume from the interstitial to the intravascular compartment.

Several studies [2–4], but not all [5] found a reduced incidence in IDH or decline in BP in patients treated with conventional (138–140 mmol/l) compared to low (i.e. ≤135 mmol/l) dialysate sodium concentrations.

High sodium (i.e. ≤144 mmol/l) dialysate has also been assessed in the prevention of IDH. Whereas high sodium dialysate was found to be useful in the prevention of IDH in some [6,7], but not all [8] studies, it was also associated with worsened intra-dialytic BP control, especially in hypertensive patients [6], or increased inter-dialytic weight gain [8].

With sodium profiling, dialysate sodium is modelled during dialysis in order to reduce the decline in blood volume during ultrafiltration. The possibility for sodium profiling is present on most dialysis modules and easy to apply. However, available studies differ widely with regard to mean dialysate sodium concentration and type of sodium profiles. With most sodium profiles, the mean dialysate sodium concentration is

higher (>142 mmol/l) than conventionally used dialysate sodium concentrations (138–140 mmol/l). Sodium profiles can be divided into linearly or stepwise increasing or decreasing profiles, and alternated high–low profiles.

Most studies, but not all [9,10] found sodium profiling to be of use in the prevention of haemodynamic instability during dialysis [6,11–14,17]. However, follow-up time in most studies was short. One study found sodium profiling to be efficacious in only 22% of patients [15].

In most studies, sodium profiles were not combined with ultrafiltration profiling. In a recent study, different sodium profiles with or without ultrafiltration profiling were compared. In general, sodium profiling appeared to be more efficacious when performed in combination with ultrafiltration profiling [13].

The increased dialysate sodium concentration in the prevention of IDH may be of greater importance than the use of the profile per se, as one study did not find a difference in incidence of IDH between sodium profiled treatments and haemodialysis with a mean dialysate sodium concentration of 143 mmol/l [16].

In many [8,9,11,12,15,17–19], but not all studies [10,14,18], sodium profile or high sodium dialysis was associated with an increase in thirst, inter-dialytic weight gain and higher pre-dialysis BP levels, although not all side effects occurred concomitantly in the available studies When the dialysate sodium concentration is higher than the plasma sodium concentration corrected for the Donnan factor, net inward diffusion of sodium from dialysate to plasma is to be expected [19]. One study compared the efficacy of sodium profile and high sodium dialysis with cool dialysis [6]. Whereas treatment tolerance was improved with sodium profile, high sodium dialysis and cool dialysis compared with standard dialysis, no difference between the different experimental strategies was observed.

Some studies assessed the effect of so-called sodium-neutral profiles (in which mean dialysate sodium concentration is comparable with conventionally used sodium concentrations) on haemodynamic stability. Three studies found a smaller decline in the intradialytic BP fall or a reduction in IDH during the sodium neutral profile [20–22]. In one randomized cross-over study the incidence of complicated treatments was less pronounced with a sodium neutral profile when combined with ultrafiltration profiling, but not when performed without an ultrafiltration profile [13]. In two other studies no benefits were observed [16,23]. Due to the conflicting evidence, no recommendation regarding sodium neutral profiles can yet be made.

Individualizing dialysate sodium to the plasma sodium concentration of the dialysate may improve haemodynamic stability during dialysis [24]. However, this approach would appear difficult to perform in daily clinical practice.

It has also become possible to model changes in plasma conductivity, as a surrogate of dialysate sodium. Recent small studies have addressed the effects of conductivity controlled feedback or prescription of dialysate conductivity based on mathematical models in the prevention of IDH. Although a beneficial effect of conductivity adjustments based on mathematical models was observed, this methodology appears too complicated to perform in daily practice [25]. The usefulness of an automatic algorithm for control of plasma conductivity was studied during paired filtration dialysis, and resulted in a decrease in IDH without negative effects on sodium balance [26]. However, the possibility for plasma conductivity controlled feedback is only possible on a limited number of dialysis modules, and has not been studied systematically during haemodialysis. A preliminary study showed no reduction in IDH with the use of plasma conductivity controlled feedback [27].

Summarizing, most studies, but not all, found high sodium dialysate or sodium profiles to be effective in the prevention of IDH. However, several studies showed increased inter-dialytic weight gain, hypertension and thirst with sodium profiles (level II). Evidence on so-called sodium-neutral profiles is still limited. However, especially when used in combination with ultrafiltration profiling, beneficial effects were observed in some studies. Individualization of dialysate sodium appears promising, but clinical evidence is still limited. From the data available, no difference in efficacy was observed between sodium profiling and non-profiled high sodium dialysis.

Recommendation for research

To investigate the role of plasma conductivity controlled feedback and sodium neutral profiles in the prevention of IDH. To compare the effects of high sodium dialysis or sodium profiling with standard sodium dialysis on cardiovascular morbidity and mortality.

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3.2.2 Dialysate buffer

- **Guideline 3.2.2 Bicarbonate dialysis should be used to prevent IDH (Evidence level III).**

Rationale

Acetate, in the past frequently used as dialysate buffer, has both vasodilating and cardiodepressant effects [1–3]. In various small cross-over studies, a larger decline in BP or higher incidence of IDH were observed with the use of acetate compared with bicarbonate [2,4–7], whereas in one study fewer therapeutic interventions were needed with bicarbonate dialysis [8]. One controlled study showed that ultrafiltration tolerance was significantly increased by using bicarbonate instead of acetate as dialysate buffer [9]. Two studies assessed the effect of a change in dialysate buffer from bicarbonate to acetate in their entire population [10,11]. In one of them, a non-randomized cross-over trial in which the authors switched their entire population from acetate to bicarbonate dialysis, a 50% decrease in the incidence of IDH was observed [11]. Also during haemodiafiltration, less haemodynamic instability was observed with the use of bicarbonate *vs* acetate as dialysate buffer [12].

Moreover, it has been suggested that dialysate bicarbonate concentrations might influence haemodynamic stability, as alkalaemia may result in a decrease in serum ionized calcium levels [13]. In this randomized cross-over trial, the incidence of IDH was significantly less with a dialysate bicarbonate of 26- *vs* 32 mmol/l. However, in this trial, also a low dialysate calcium (1.25 mmol/l) concentration was used [13]. In a more recent randomized cross-over trial by the same group, no difference in haemodynamic instability or BP decline was observed when patients were treated with either dialysate bicarbonate concentrations of 26 or 32 mmol/l, even when a low calcium dialysate concentration (1.25 mmol/l) was used. In this trial, the incidence of IDH was lowest when patients were treated with a dialysate bicarbonate concentration of 32 mmol/l and a dialysate calcium concentration of 1.50 mmol/l [14].

Low dialysate bicarbonate concentrations may result in insufficient correction of acidosis with adverse effects on bone metabolism and nutritional state (see EBPG guideline on nutrition/calcium phosphate metabolism).

With bicarbonate dialysis, also a small amount of acetate is present in the dialysate, and this leads to significant intra-treatment acetate transfer in HD [15] and, particularly so, in HDF [16], although the clinical relevance of this phenomenon is as yet unknown. With acetate-free biofiltration, a modified haemodiafiltration technique, no acetate is present in the

dialysate. Nitric oxide production, cytokine activation as well as neutrophil activation were found to be less during acetate free biofiltration compared with acetate dialysis as well as bicarbonate dialysis containing small amounts of acetate [5,17,18].

Acetate free biofiltration was shown to be of benefit in the reduction of IDH in some, but not all papers. However, also the convective principle of acetate free biofiltration and sodium infusion might influence haemodynamic stability (see Dialysate and body temperature), making it difficult to discriminate between the effects of absence of acetate and the other effects.

Summarizing, the decline in BP and incidence of IDH is higher with the use of acetate as dialysate buffer. Standard bicarbonate concentrations have no haemodynamic disadvantage compared with low dialysate bicarbonate concentrations if a dialysate calcium concentration of 1.50 mmol/l is used.

Recommendations for research

To investigate the role of acetate-free on-line haemo(dia)filtration on NO-cytokine synthesis and IDH.

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3.2.3 Dialysate calcium

- **Guideline 3.2.3 The use of a dialysate calcium concentration of 1.50 mmol/l should be considered in patients with frequent episodes of IDH, unless contra-indications are present (Evidence level II).**

Rationale

Changes in ionized calcium play a pivotal role in myocardial contractility during dialysis. Several studies showed a lower myocardial contractility between patients treated with a low (1.25 mmol/l) compared with patients treated with a high (1.75 mmol/l) dialysate calcium concentration [1,2]. Moreover, the change in mean arterial pressure during dialysis was inversely related to the change in ionized calcium levels [3] whereas in two studies, one of which was performed in cardiac compromised patients the decline in BP was less with the dialysate concentration of 1.75 mmol/l compared with 1.25 mmol/l [2,4]. In another study, no difference in the BP response was observed between high- and low-calcium dialysate [5]. On, the other hand, high-calcium dialysate leads in general to a positive calcium balance during dialysis, whereas calcium balance is generally negative with low calcium dialysate [6]. High calcium dialysate may have short-term adverse effects on arterial stiffness and cardiac relaxation [3,8], although another study did not find an effect of an increase in ionized calcium levels during high-calcium dialysis on diastolic function of the heart [9]. The relation between dialysate calcium concentration and vascular calcifications has not yet been studied.

A dialysate calcium concentration of 1.50 mmol/l has less pronounced effects on calcium balance compared with dialysate calcium concentrations of respectively 1.25 or 1.75 mmol/l. In general, also depending on ultrafiltration, calcium balance is slightly negative with

a dialysate calcium concentration of 1.50 mmol/l [6], although in patients with low pre-dialytic plasma calcium levels, a positive calcium balance may occur with the use of 1.50 mmol/l and even 1.25 mmol/l [10]

A randomized cross-over study found a lower incidence of IDH and less decline in BP with the use of a dialysate calcium concentration of 1.50 mmol/l compared with low-calcium dialysis. In this study, dialysate bicarbonate concentration was 26 mmol/l during low-calcium dialysis and 32 mmol/l with the dialysate calcium concentration of 1.50 mmol/l [11] (see also dialysate buffer).

Another randomized cross-over study assessed the effect of calcium profiling on haemodynamic stability during dialysis in 18 patients. During a 9-week period, three treatments differing in dialysate calcium concentration were applied, respectively 1.25 mmol/l, 1.50 mmol/l and a profiled treatment with a calcium concentration of 1.25 mmol/l during the first 2 h and 1.75 mmol/l during the remaining 2 h. With the profiled treatment, intra-dialytic events were reduced compared with the treatments with dialysate calcium concentrations of 1.25 mmol/l and 1.50 mmol/l [12]. No studies have been performed comparing a dialysate calcium concentration of 1.50 mmol/l with a dialysate calcium concentration of 1.75 mmol/l.

It is recognized by the working group that the K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease advise a routine prescription of dialysate calcium concentration of 1.25 mmol/l [13]. In the opinion of the working group, the potential benefits of 1.25 dialysate calcium concentrations on vascular calcification should be balanced against the negative effects on haemodynamic stability in patients with frequent episodes of IDH.

Summarizing, most studies showed a positive effect of high calcium dialysate on haemodynamic stability during dialysis compared with low-calcium dialysate. However, high calcium dialysate may lead to positive calcium balance in short- and long-term, with the potential for adverse effects. One study showed a decline in IDH with the use of a dialysate calcium concentration of 1.50 mmol/l compared with low calcium dialysis Few other studies compared the haemodynamic effects of a dialysate calcium concentration of 1.5 mmol/l with high- or low-calcium dialysate.

Recommendations for research

To perform further studies on the effects of dialysate calcium concentration (1.50 mmol/l *vs* high or low calcium dialysate) on IDH. To perform studies on the effects of dialysate calcium concentration on vascular calcification.

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3.2.4 Other dialysate components

- **Guideline 3.2.4a In patients with frequent episodes of IDH, low (0.25 mmol/l) magnesium dialysate should be avoided, especially in combination with low-calcium dialysate (Level II).**

- **Guideline 3.2.4b Glucose-free dialysate concentrations should be avoided in diabetics (Opinion).**

Rationale

Also other components of the dialysate may influence haemodynamic stability during dialysis. In diabetic patients, one randomized cross-over study found a reduced incidence of IDH and a reduction of hypoglycaemic episodes with a higher (11 mmol/l) compared with a conventional (5.5 mmol/l) glucose concentration of the dialysate [1]. However, the EBPG working group felt that further research is needed before definite recommendations regarding dialysate glucose prescription in diabetic patients could be made, as the prescription of high (11 mmol/l = 2 g/dl) glucose dialysate only for diabetic patients would necessitate relatively large changes in the organization of the

dialysis clinic. At present, it would appear rational to refrain from the use of glucose-free dialysate in diabetic patients. No study has assessed the role of dialysate glucose concentrations in non-diabetic patients.

Also a low magnesium (0.25 mmol/l) concentration of the dialysate was associated with a larger decline in BP and higher frequency of IDH compared with a higher dialysate magnesium concentration (0.75 mmol/l), especially in association with a low-calcium dialysate [2].

Dialysate potassium concentration was found to have an effect on inter-dialytic BP, but not on intra-dialytic BP [3].

Summarizing, there is limited evidence that other dialysate components, such as glucose (diabetics) and magnesium may influence the BP response during dialysis. No effect of dialysate potassium on intra-dialytic haemodynamics was observed.

Recommendations for research

To perform further studies on the effects of different dialysate glucose concentrations on the incidence of IDH in diabetic patients.

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3.3 Dialysis membranes and contamination of dialysate

- **Guideline 3.3 No particular dialysis membranes should be preferred to prevent IDH (Level II).**

Rationale

With unmodified cellulosic membranes, the activation of mononuclear cells and resulting generation of cytokines is higher compared with biocompatible membranes. It has been suggested that this phenomenon might play a role in the pathogenesis of IDH by impairing the vascular response to a decline in blood volume [1]. One multicenter double-blind RCT compared the effects of high-flux polysulfone with a low-flux cuprophane membrane on acute intra-dialytic complications [2]. The incidence of IDH was similar with high-flux polysulfone (23.8%) and low-flux cuprophan membranes. Other prospective randomized cross-over trials also did not show a difference in IDH between cuprophane and high- or low-flux synthetic membranes (19 *vs* 22%) [3–5]. In one study, an increase in intradialytic symptoms, but not of IDH, was observed with cuprophane compared with polysulfone low-flux membranes [6]. No study has yet compared the haemodynamic effects of low- *vs* high-flux membranes with the same biocompatibility characteristics.

Contaminated dialysate may stimulate the formation of vasoactive cytokines through activitation of monocytes. No studies have addressed the effect of dialysate contamination on IDH. In one study, no difference in vascular reactivity was observed among patients treated with ultrapure dialysate or contaminated dialysate [7]. However, this study did not address the effect of ultrapure dialysate on IDH *per se*.

Summarizing, there is no evidence that biocompatible membranes have a beneficial effect in the prevention for IDH. No studies have been performed assessing the effects of ultrapure dialysate on IDH.

Recommendations for research

To assess the effect of ultrapure dialysate on IDH.

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3.4 Dialysate and body temperature

- **Guideline 3.4.1 Cool dialysate temperature dialysis (35–36°C) or isothermic treatments by blood temperature controlled feedback should be prescribed in patients with frequent episodes of IDH (Evidence level I).**
- **Guideline 3.4.2 With cool temperature dialysis, dialysate temperature should be gradually reduced in steps of 0.5°C from 36.5°C until symptoms are controlled (Opinion).**
- **Guideline 3.4.3 Dialysate temperatures <35°C should not be used (Opinion).**

Rationale

During haemodialysis with standard dialysis temperatures (≥37°C), core temperature increases despite net energy loss over the extracorporeal system [1–6]. This phenomenon is not fully understood. It may be partly due to reduced heat loss from the skin resulting from vasoconstriction in response to a decline in blood volume [3]. The increase in core temperature leads to subsequent dilatation of resistance and capacitance vessels in the skin, antagonizing the physiologic response to hypovolaemia [7]. However, this hypothesis has recently been challenged [8]. In order to prevent this increase in core temperature, a significant amount of thermal energy, amounting to 30% of daily resting energy expenditure, has to be removed by the extracorporeal circuit by cooling the dialysate [9]. Various randomized cross-over trials showed that dialysis with cooler dialysate temperatures (in most studies 35°C) was associated with improved reactivity of peripheral resistance and capacitance vessels, increased myocardial contractility [10], reduced BP decline and reduced frequency of IDH compared with dialysis with dialysate temperatures of 37–37.5° [5,11–20]. Most studies were of relatively short duration. Only one small study compared cool dialysis with dialysate temperatures <37°C. In this study, an improvement in patients perception of haemodialysis and reduced decline in BP was observed when patients were dialysed against a dialysate temperature of 35°C compared with 36.5°C [21].

Cool temperature dialysis was found to be equally effective in the prevention of IDH compared with sodium profiling [12] and use of midodrine [22]. In a recent systematic review, 22 studies comprising 408 patients were assessed (in 16 studies, the effects of a fixed low dialysate temperature were assessed, whereas six studies addressed blood temperature controlled treatments). Pooling all these studies, IDH occurred 7.1 times less frequently with cool or blood temperature controlled dialysis, whereas post-dialysis mean arterial pressure was 11.3 mmHg higher compared with standard dialysate temperature [23].

Cool dialysis may lead to shivering. Moreover, in two [1,4], but not in other studies [2,18], the decline in blood volume was significantly larger during cool dialysis, possibly due to reduced refill of blood volume from the interstitium due to peripheral vasoconstriction. Still, even in the study in which the decline in blood volume was larger during cool dialysis, haemodynamic stability was improved compared with standard temperature dialysis [4]. No effect on urea kinetics was observed during cool dialysis [15,18].

It is not well known whether it is sufficient to prevent the increase in core temperature or whether better results are obtained when the core temperature of the patient is decreased. Moreover, the optimal dialysis temperature is not known, and may depend upon the pre-dialytic core temperature of the patient [24]. As cool dialysis may occasionally lead to shivering, the working group advises to gradually lower dialysate temperature from 36.5°C downwards during different dialysis sessions in order to achieve the best clinical result in individual patients. In order to reduce potential side effects and because of limited experience and unproven benefit of dialysate temperatures <35°C, the working group felt that dialysate temperatures <35°C should not be used.

The increase in core temperature during dialysis may be prevented without cooling the patient by feedback technology. One randomized cross-over multicentre study showed a markedly reduced incidence (−50%) of IDH with controlled extracorporeal blood cooling by feedback technology, by which the increase in core temperature was prevented (isothermic treatments) [1]. However, at present temperature controlled feedback is not yet an option present on the majority of dialysis modules.

Summarizing, cool temperature dialysis and temperature controlled feedback are effective in preventing IDH without clinically significant side effects. In order to reduce side effects such as shivering, the panel advises to reduce dialysate temperature from 36.5°C downward until an optimal effect is reached. There is limited evidence and unproven benefit of reducing dialysate temperatures <35°C.

Recommendations for research

To compare the effects of cool temperature dialysis and temperature controlled feedback on IDH and side effects.

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3.5 Convective techniques and isolated ultrafiltration

- **Guideline 3.5.1 Haemo(dia)filtration techniques should not be considered a first-line option for the prevention of IDH, but as a possible alternative to cool dialysis (Evidence level II).**

Rationale

Various randomized and non-randomized cross-over trials found a reduced incidence of IDH and lesser decline in BP during convective therapies compared with HD. This holds true for (on-line) haemofiltration, haemodiafiltration and acetate-free biofiltration [1–5].

However, other studies did not find a reduction in IDH with haemodiafiltration or acetate-free biofiltration compared with bicarbonate dialysis [6,7]. Also, a recent systematic review, in which only a limited number of studies were included, did not show differences in IDH between haemodialysis and convective treatments [8]. Still, the reactivity of resistance and capacitance vessels during convective therapies is superior compared with standard haemodialysis sessions [1,9].

There has been discussion about the physiologic mechanisms of the improved vascular response during convective therapies. Some studies showed different effects of haemodialysis and haemofiltration on sodium balance [10,11]. Although an increased removal of vasodepressor substances has been hypothesized [9], extracorporeal cooling during haemofiltration is larger compared with haemodialysis [12,13], which has a profound effect on vascular reactivity [14] (see Dialysis and body temperature). This even holds true for on-line haemodiafiltration, because of additional energy loss from the substitution line [15,16]. When matched for thermal energy transfer, the decline in BP or incidence of IDH was found to be comparable to dialysis and haemo(dia)filtration [15,17–19]. Thus, it appears that with cooling of the dialysate, the same haemodynamic response can be obtained during haemodialysis as compared with convective treatments. However, except from [15], all of the studies performed on this subject were short-term. Trials comparing haemodynamic tolerance between different convective techniques are scarce. In one cross-over trial, the incidence of IDH was less during on-line haemofiltration compared with on-line haemodiafiltration [20]. However, extracorporeal blood cooling is larger during on-line haemofiltration compared with on-line haemodiafiltration [16]. Also, extracorporeal blood cooling will depend on the place of infusion and will be larger in the pre-dilution compared with the post-dilution mode [16].

Summarizing, in various studies, the incidence of IDH was found to be less during convective techniques compared with conventional haemodialysis treatment, However, no difference in IDH or intra-dialytic BP decline was observed when haemodialysis and convective treatments were matched for thermal and other confounding factors.

Recommendation for research

Perform long-term randomized studies including on-line HF, on-line HDF and haemodialysis to assess their respective effect on IDH when thermally matched.

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- **Guideline 3.5.2 Sequential isolated ultrafiltration followed by isovolemic dialysis should not be used as a regular strategy for the prevention of IDH (Evidence level II).**

Rationale

During isolated ultrafiltration, the constriction of resistance and capacitance vessels is superior compared with standard haemodialysis treatment [1–3]. However, this difference appears to be minimized when haemodialysis and isolated ultrafiltration are thermally matched [4–7]. In one randomized cross-over study, the effect of isolated ultrafiltration (1 h followed by 3 h of isovoalemic dialysis) was compared with standard haemodialysis, high sodium dialysis, sodium profiling or cool temperature dialysis [8]. The incidence of IDH was significantly higher during isolated ultrafiltration compared with the other experimental protocols, possibly because of the high ultrafiltration rates. It should be stated that in this study, all the volume was removed during isolated ultrafiltration followed by isovolaemic haemodialysis, resulting in very high ultrafiltration rates during the initial procedure.

Summarizing, isolated ultrafiltration followed by isovolaemic dialysis may actually increase the risk for IDH because of the high ultrafiltration rates.

Recommendation for research

To compare the haemodynamic effects of more gradual ultrafiltration rates during isolated ultrafiltration, followed by ultrafiltration combined with haemodialysis with those of cool dialysis.

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3.6 Dialysis duration and frequency

- **Guideline 3.6 A prolongation in dialysis time or an increase in dialysis frequency should be considered in patients with frequent episodes of IDH (Levels II–III).**

Rationale

Increasing dialysis time enables the reduction of ultrafiltration rate, which will lead to a more gradual decline in blood volume. Studies towards the effect of prolonging dialysis time on IDH are scarce, however. One randomized cross-over trial assessed the effects of 4 *vs* 5 h treatment time on intra-dialytic tolerance and found a reduction in hypotensive episodes [1]. Moreover, the effects of a reduction of ultrafiltration rate, which can only be achieved by prolonging dialysis time, was studied in cardiac compromised patients. In this study, a less pronounced fall in SBP was observed with an UF-rate of 500 compared with an UF rate of 1000 ml/h [2]. In DOPPS, the incidence of IDH was ±30% less in patients with prescribed UF rates <11 ml/kg/h compared with patients with higher presecribed UF rates [3]. Also mortality was lower in patients treated with UF rates <10 ml/kg/h [3]. In patients dialysed 8 h for three times weekly, the incidence of hypotension was found to be very low [4].

With more frequent dialysis, such as quotidian dialysis or short daily dialysis, BP is better controlled and left ventricular mass is reduced [5]. Because of the more frequent sessions, ultrafiltration volume is reduced [5]. One non-randomized cross-over study [6] showed a reduction in IDH by a change from three times 4 h per week to six times weekly 2 h dialysis sessions. Another cross-over study also showed a reduction in the need for saline infusion after conversion from thrice weekly dialysis sessions to six times weekly 2 h sessions [7]. In a cohort study, 23 patients (11 patients, short daily HD; 12 patients, long nocturnal HD) were compared with 22 conventional thrice-weekly HD patients serving as controls. A reduced incidence in dialysis-related symptoms was observed in patients treated with short daily HD [8]. However, in the study by Fagugli *et al*. including stable patients, no difference in IDH was observed between short daily haemodialysis and standard thrice-weekly dialysis [5].

Summarizing, available evidence shows that prolonging dialysis time may result in the reduction of IDH, whereas a reduction in ultrafiltration rate resulted in a less pronounced decline in systolic BP in patients with compromised cardiac function.

The scarce available evidence suggests that IDH can be reduced by more frequent dialysis sessions. However, for logistic reasons, this approach may not be possible yet or at least difficult to achieve in a substantial part of dialysis units.

Recommendation for research

Perform randomized studies towards the effect of more frequent dialysis on IDH.

References

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3.7 Switch to peritoneal dialysis

- **Guideline 3.7 A treatment change to peritoneal dialysis should be considered in patients who remain refractory to interventions for the prevention of IDH (Opinion).**

Rationale

Due to its (semi)continuous nature, peritoneal dialysis leads to more gradual fluid removal compared with intermittent haemodialysis and would, therefore, appear preferable in patients with intractable dialysis hypotension. However, no studies assessed the effects of a treatment change from haemodialysis to peritoneal dialysis on the propensity to hypotension.

Summarizing, there are no studies evaluating the effects of a shift from HD to PD on IDH.

Recommendations for research

Study the incidence of symptomatic hypotension after patients have switched treatment from haemodialysis

to peritoneal dialysis (also if for other reasons than refractory hypotension).

4. Avoidance of antihypertensive drugs and prescription of vasoactive medication before dialysis

- **Guideline 4.1 In patients with frequent episodes of IDH, antihypertensive agents should be given with caution prior to dialysis depending on pharmacodynamics, but should not be routinely withheld on the day of haemodialysis treatment (Evidence level III).**

Rationale

Stepwise reduction of antihypertensive agents is necessary to achieve dry weight in dialysis patients [1,2]. However, it may be necessary to continue vasoactive agents in individual dialysis patients (beta blocking agents, angiotensin converting enzyme inhibitors, angiotensin receptor blocking agents) due to co-existing cardiovascular disease or persistent volume-independent hypertension.

There is limited evidence about the effect of antihypertensive agents on IDH. In one large cohort study, calcium antagonists or ACE inhibitors were not a predictor for the risk of frequent IDH episodes, whereas the use of nitrates was an independent risk factor [3]. However, from these data, no causal relationships can be estimated. One randomized cross-over study did not find a difference in IDH between patients receiving a pre-dialytic dose of verapamil *vs* placebo [4]. Another randomized cross-over trial found post-dialytic orthostatic hypotension in all haemodialysis patients given (the very high dose of) 100 mg captopril after dialysis [5]. Although the effect of such agents on IDH has not been adequately studied, it would appear rational not to give short-acting antihypertensive agents immediately before a dialysis session.

Summarizing, there is no evidence that routinely withholding antihypertensive treatment on the day of dialysis treatment is of benefit in the prevention of IDH. The use of nitrates was independently associated with risk of frequent IDH episodes, although a cause or effect relationship from these data cannot be estimated.

Recommendation for research

Assess the effect of withholding antihypertensive treatment on the day of dialysis on IDH and inter-dialytic BP control. Assess the effect of different dosing schedules on the same parameters.

References

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- **Guideline 4.2 Midodrine should be considered if other treatment options have failed (Evidence level I).**

Rationale

Midodrine is an oral alpha-1 agonist. The metabolite of midodrine, desglymidodrine, induces constriction of both resistance and capacitance vessels.

In a systematic review including 37 papers, the effectiveness of midodrine was assessed [1]. In the included studies the dose of midodrine varied between 2.5 and 10 mg before dialysis. The mean nadir systolic BP was 13 mmHg higher compared with placebo. Ten studies assessed the role of midodrine in the prevention of IDH, of which six showed an improvement in symptoms [1]. Side effects reported are scalp parestehesias, heartburn, flushing, headache, neck pain and weakness.

One study compared the effectiveness of midodrine compared to cool dialysis [2]. Both cool dialysis and midodrine appeared to be effective in the prevention of IDH, whereas no difference in the BP response or incidence of IDH was observed between the two therapies. No additive effect of the combination of both therapies was shown.

It should be mentioned that midodrine is not registered for this indication in all European countries. Moreover, long-term safety in dialysis patients has not been assessed.

The effectiveness of various vasoactive drugs in the prevention of IDH has been assessed. Data on the effectiveness and safety of l-DOPS, lysine vasopressine, ergotamine, methylene blue and dobutamine are limited and insufficient to make firm recommendations [3–7]. Data on sertralin, a serotonin reuptake inhibitor, are controversial [8,9]. Recently, a randomized trial showed a reduction in IDH with continuous infusion of vasopressin during dialysis [10].

Summarizing, Midodrine (starting dose 2.5 mg 30 min before dialysis, maximal dose 10 mg) is effective and probably safe in preventing IDH, although data on long-term safety are lacking. However, the superiority of midodrine above other interventions has not yet been shown. Evidence for the effectiveness and safety of other vasoactive drugs is limited.

Recommendations for research

To compare the effect of midodrine and cool dialysis in larger long-term randomized studies.

References

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- **Guideline 4.3 L-carnitine supplementation should be considered for the prevention of IDH if other treatment options have failed (Evidence level III).**

In haemodialysis patients, L-carnitine levels may be low because of reduced biosynthesis in the kidney and losses in the dialysate. L-carnitine deficiency may lead to reduced systolic function of the heart. In an uncontrolled study, L-carnitine supplementation resulted in an improvement in left ventricular ejection fraction [1]. In another study, a relation between low carnitine levels and IDH was observed [2]. One randomized study showed an improvement in IDH after L-carnitine supplementation [3]. However, in this study, haemodynamic stability was one of many endpoints. Moreover, no further studies have assessed the effects of L-carnitine supplementation on IDH.

It is not known whether the potential beneficial effects of L-carnitine supplementations on IDH are restricted to patients with reduced left ventricular systolic function or those with reduced plasma carnitine levels.

In view of these uncertainties and the limited evidence on the potential beneficial effects of L-carnitine supplementation on IDH, the working group felt that other strategies should be attempted before L-carnitine supplementation (20 mg/kg at the end of each dialysis session) [4] is to be considerated. From a theoretical point of view, carnitine supplementation may be beneficial in patients with otherwise unexplained systolic dysfunction and IDH.

Summarizing, there is limited evidence that l-carnitine supplementation is beneficial in the prevention of IDH.

Recommendations of research

Perform more extended studies regarding the effect of l-carnitine supplementation on IDH.

References

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5. Stratified approach to prevent IDH

First-line approach

- Dietary counselling (sodium restriction).
- Refraining from food intake during dialysis.
- Clinical reassessment of dry weight.
- Use of bicarbonate as dialysis buffer.
- Use of a dialysate temperature of 36.5°C.
- Check dosing and timing of antihypertensive agents.

Second-line approach

- Try objective methods to assess dry weight.
- Perform cardiac evaluation.
- Gradual reduction of dialysate temperature from 36.5°C downward (lowest 35°C) or isothermic treatment (possible alternative: convective treatments).

- Consider individualized blood volume controlled feedback.
- Prolong dialysis time and/or increase dialysis frequency.
- Prescribe a dialysate calcium concentration of 1.50 mmol/l.

Third-line approach (only if other treatment options have failed)

- Consider midodrine.
- Consider L-carnitine supplementation.
- Consider peritoneal dialysis.

6. Treatment of IDH

6.1 Trendelenburg position

- **Guideline 6.1 The Trendelenburg position should be considered in the treatment of IDH. However, efficacy may be limited (Opinion).**

Rationale

Trendelenburg's position is very commonly applied in the treatment of IDH. With the use of this manoeuver, blood volume is believed to be centralized. Still, in normotensive volunteers, the increase in central blood volume was 1.8% [1]. In hypotensive non-uraemic patients, the Trendelenburg position did not increase BP [2]. The Trendelenburg position is widely used in the treatment of IDH. However, few studies have addressed its efficacy. In a cross-over study in dialysis patients, the increase in blood volume after Trendelenburg position was 0.4% only [3]. Data on BP changes during dialysis after the application of the Trendelenburg position are lacking.

Summarizing, the effect of the Trendelenburg position on blood volume appears to be small, whereas data on BP are lacking.

Recommendation for research

To assess the effect of the Trendelenburg position on the BP course as preventive or therapeutic manoeuver for IDH.

1. Bivins HG, Knopp R, dos Santos PA. Blood volume distribution in the Trendelenburg position. *Ann Emerg Med* 1985; 14: 641–643
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3. Coll E, Valles M, Torguet P, Bronsoms J, Mate G, Mauri JM. Evaluation of plasma volume variation during different hemodialysis maneuvers. *Nefrologia* 2004; 24: 463–469

6.2 Stopping ultrafiltration

- **Guideline 6.2 Ultrafiltration should be stopped during an episode of IDH (evidence level III).**

Rationale

Stopping ultrafiltration will prevent a further decline in blood volume and may facilitate refill of blood volume from the interstitial compartment. Stopping ultrafiltration resulted in an increase in blood volume of 2–2.3% [1]. Data on the BP response to this manoeuver are lacking. Slowing blood flow rate is also sometimes used in the treatment of IDH. However, no data are present that assessed the effect of this manoeuver on the BP response. In a randomized cross-over study, no difference in left ventricular function was observed between treatment sessions with respective blood flow rates of 250, 350 or 450 ml/min [2].

Summarizing, stopping ultrafiltration during IDH may result in an increase in blood volume. No effects of different blood flow rates on haemodynamic parameters have been reported.

Recommendation for research

To assess the effect of adjusting blood flow rate on the BP course and as preventing manoeuver or therapy for IDH.

1. Coll E, Valles M, Torguet P, Bronsoms J, Mate G, Mauri JM. Evaluation of plasma volume variation during different hemodialysis maneuvers. *Nefrologia* 2004; 24: 463–469
2. Alfurayh O, Galal O, Sobh M *et al*. The effect of extracorporeal high blood flow rate on left ventricular function during hemodialysis–an echocardiographic study. *Clin Cardiol* 1993; 16: 791–795

6.3 Infusion fluids

- **Guideline 6.3.1 Isotonic saline should be infused in patients unresponsive to stopping ultrafiltration and Trendelenburg's position during an episode of IDH (Evidence level II).**

- **Guideline 6.3.2 Infusion of colloid solutions should be considered n patients who remain unresponsive to saline infusion (Evidence level III).**

Rationale

In patients who are unresponsive to Trendelenburg's position and stopping ultrafiltration, infusion fluids are commonly used to increase blood volume during an episode of IDH. Both crystalloid and colloid solutions have been studied in the treatment of IDH.

Several studies have assessed the effect isotonic saline, hypertonic saline, hypertonic glucose, mannitol and colloid solutions. In a study in six stable dialysis patients, which compared the effects of isovolumetric infusions of glucose 5 and 20%, saline 0.9 and 3.0% and mannitol 20% on blood volume during ultrafiltration, the increase in blood volume was largest during the hypertonic glucose solutions [1]. In another study, the increase in blood volume was larger after the infusion of

100 ml of the plasma expander gelofusine compared with 100 ml isotonic saline, whereas the increase in blood volume was in turn larger after infusion of 100 ml of isotonic (0.9%) saline compared with 10 ml of hypertonic (20%) saline [2]. In another study in 10 stable dialysis patients, the effects of hydroxy-ethyl-starch (HES) 10% and albumin 5% on blood volume were superior compared with isotonic saline [3].

Effects of hypertonic glucose, mannitol, and gelofusine have not been studied in hypotensive-prone dialysis patients.

One randomized controlled trial in 72 patients did not find a difference in efficacy between albumin and 0.9% saline infusion in the treatment of IDH [4]. In contrast, another randomized study showed an improved BP response with a dextran/hypertonic saline combination compared with hypertonic saline (3%) alone.

Also, in patients prone to hypotensive episodes, the BP response with hydroxyethylstarch 10% was found to be superior to hypertonic saline, and did not differ significantly from albumin infusion [5]. Given in large doses, hydroxy-ethyl starch (HES) may accumulate in patients with renal failure. HES may accumulate in patients with renal failure, as the elimination time is 3-fold prolonged. However, a dose of 100 ml HES 10%/week appears to be safe [5].

Summary of evidence

In a randomized study, both isotonic saline and albumin solutions were effective in the treatment of IDH. Evidence with regard to the relative efficacy of crystalloid and colloid solutions is conflicting. Hypertonic saline does not appear to be more efficacious than isotonic saline. Albumin does not appear to be superior to hydroxyethylstarch in the treatment of IDH.

Recommendation for research

To perform randomized studies to compare the efficacy of isotonic saline and hydroxyl-ethyl starch in the treatment of IDH.

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5. Van der Sande FM, Luik AJ, Kooman JP, Verstappen V, Leunissen KM. Effect of intravenous fluids on blood pressure course during hemodialysis in hypotensive-prone patients. *J Am Soc Nephrol* 2000; 11: 550–555

6.4 Protocol-based treatment

- **Guideline 6.4 The development a centre-specific protocol, with stepwise interventions for the treatment of IHD should be considered (Evidence level III).**

Rationale

Emily *et al.* prescribed the stepwise infusion of isotonic and hypertonic saline, followed by mannitol infusion if the effect was insufficient, before albumin was infused. Using this treatment protocol, the authors were able to reduce the use of albumin from 11% to 6% [1].

Summarizing, a centre-specific protocol leads to a reduction in the use of albumin solutions.

Recommendation for research

To perform additional studies towards the cost effectiveness of protocol-based interventions for the treatment of IDH.

1. Emili S, Black NA, Paul RV, Rexing CJ, Ullian ME. A protocol-based treatment for intradialytic hypotension in hospitalized hemodialysis patients. *Am J Kidney Dis* 1999; 33: 1107–1114

Conflict of interest statement: J.K. received research grants and fees for invited lectures from Baxter, Fresenius and Gambro. Moreover, he received fees for invited lectures from Amgen. A.B. is Chief of Advisory Board of Fresenius for Turkish FMC Clinics and Country Medical Representative. F.P. received research grants and fees for invited lectures from Bellco and fees for invited lectures from Fresenius and Gambro.

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