

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.

References

- Leunissen KM, Cheriex EC, Janssen J *et al.* Influence of left ventricular function on changes in plasma volume during acetate and bicarbonate dialysis. *Nephrol Dial Transplant* 1987; 2: 99–103
- Baldamus CA, Ernst W, Frei U, Koch KM. Sympathetic and hemodynamic response to volume removal during different forms of renal replacement therapy. *Nephron* 1982; 31: 324–332
- Veech RL. The untoward effects of the anions of dialysis fluids. *Kidney Int* 1988; 34: 587–597
- Malberti F, Surian M, Colussi G, Minetti L. The influence of dialysis fluid composition on dialysis tolerance. *Nephrol Dial Transplant* 1987; 2: 93–98
- Noris M, Todeschini M, Casiraghi F *et al.* Effect of acetate, bicarbonate dialysis, and acetate-free biofiltration on nitric oxide synthesis: implications for dialysis hypotension. *Am J Kidney Dis* 1998; 32: 115–124
- Leenen FH, Buda AJ, Smith DL, Farrel S, Levine DZ, Uldall PR. Hemodynamic changes during acetate and bicarbonate hemodialysis. *Artif Organs* 1984; 8: 411–417
- Hakim RM, Pontzer MA, Tilton D, Lazarus JM, Gottlieb MN. Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients. *Kidney Int* 1985; 28: 535–540
- Henrich WL, Woodard TD, Meyer BD, Chappell TR, Rubin LJ. High sodium bicarbonate and acetate hemodialysis: double-blind crossover comparison of hemodynamic and ventilatory effects. *Kidney Int* 1983; 24: 240–245
- Graefe U, Milutinovich J, Follette WC, Vizzo JE, Babb AL, Scribner BH. Less dialysis-induced morbidity and vascular instability with bicarbonate in dialysate. *Ann Intern Med* 1978; 88: 332–336
- Mastrangelo F, Rizzelli S, Corliano C *et al.* Benefits of bicarbonate dialysis. *Kidney Int* 1985; 17 [Suppl]: S188–S193
- Man NK, Fournier G, Thireau P, Gaillard JL, Funck-Brentano JL. Effect of bicarbonate-containing dialysate on chronic hemodialysis patients: a comparative study. *Artif Organs* 1982; 6: 421–428
- Biasioli S, Feriani M, Chiaramonte S *et al.* Different buffers for hemodiafiltration: a controlled study. *Int J Artif Organs* 1989; 12: 25–30
- Gabutti L, Ferrari N, Giudici G, Mombelli G, Marone C. Unexpected haemodynamic instability associated with standard bicarbonate haemodialysis. *Nephrol Dial Transplant* 2003; 18: 2369–2376
- Gabutti L, Ross V, Duchini F, Mombelli G, Marone C. Does bicarbonate transfer have relevant hemodynamic consequences in standard hemodialysis? *Blood Purif* 2005; 23: 365–372
- Fournier G, Potier J, Thebaud HM *et al.* Substitution of acetic acid for hydrochloric acid in the bicarbonate buffered dialysate. *Artif Organs* 1998; 22: 608–613
- Pizzarelli F, Cerrai T, Dattolo P, Ferro G. On-line haemodiafiltration with and without acetate. *Nephrol Dial Transplant* 2006; 21: 1648–1651
- Todeschini M, Macconi D, Fernandez NG *et al.* Effect of acetate-free biofiltration and bicarbonate hemodialysis on neutrophil activation. *Am J Kidney Dis* 2002; 40: 783–793
- Amore A, Cirina P, Mitola S *et al.* Acetate intolerance is mediated by enhanced synthesis of nitric oxide by endothelial cells. *J Am Soc Nephrol* 1997; 8: 1431–1436

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 contraindications 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.

References

1. Henrich WL, Hunt JM, Nixon JV. Increased ionized calcium and left ventricular contractility during hemodialysis. *N Engl J Med* 1984; 310: 19–23
2. van der Sande FM, Cheriex EC, van Kuijk WH, Leunissen KM. Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. *Am J Kidney Dis* 1998; 32: 125–131
3. Kyriazis J, Stamatiadis D, Mamouna A. Intradialytic and interdialytic effects of treatment with 1.25 and 1.75 Mmol/L of calcium dialysate on arterial compliance in patients on hemodialysis. *Am J Kidney Dis* 2000; 35: 1096–1103
4. Maynard JC, Cruz C, Kleerekoper M, Levin NW. Blood pressure response to changes in serum ionized calcium during hemodialysis. *Ann Int Med* 1986; 104: 358–361
5. Fabrizi F, Bacchini G, Di Filippo S, Pontoriero G, Locatelli F. Intradialytic calcium balances with different calcium dialysate levels. Effects on cardiovascular stability and parathyroid function. *Nephron* 1996; 72: 530–535
6. Malberti F, Ravani P. The choice of the dialysate calcium concentration in the management of patients on haemodialysis and haemodiafiltration. *Nephrol Dial Transplant* 2003; 18 [Suppl 7]: vii37–vii40
7. Argiles A, Kerr PG, Canaud B, Flavier JL, Mion C. Calcium kinetics and the long-term effects of lowering dialysate calcium concentration. *Kidney Int* 1993; 43: 630–640
8. Nappi SE, Saha HH, Virtanen VK, Mustonen JT, Pasternack AI. Hemodialysis with high-calcium dialysate impairs cardiac relaxation. *Kidney Int* 1999; 55: 1091–1096
9. Ie EH, Vletter WB, ten Cate FJ, Weimar W, Zietse R. Increase in serum ionized calcium during diffusive dialysis does not affect left ventricular diastolic function. *Blood Purif* 2004; 22: 469–472
10. Sigrist M, McIntyre CW. Calcium exposure and removal in chronic hemodialysis patients. *J Ren Nutr* 2006; 16: 41–46
11. Gabutti L, Ross V, Duchini F, Mombelli G, Marone C. Does bicarbonate transfer have relevant hemodynamic consequences in standard hemodialysis? *Blood Purif* 2005; 23:365–372
12. Kyriazis J, Glotsos J, Bilirakis L, Smirnioudis N, Tripolitou M, Georgiakodis F, Grimani I. Dialysate calcium profiling during hemodialysis: use and clinical implications. *Kidney Int* 2002; 61: 276–287
13. National kidney foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42 [4 Suppl 3]: S1–S201

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 intradialytic 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 intradialytic 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.

References

1. Simic-Ogrizovic S, Backus G, Mayer A, Vienken J, Djukanovic L, Kleophas W. The influence of different glucose concentrations in haemodialysis solutions on metabolism and blood pressure stability in diabetic patients. *Int J Artif Organs* 2001; 24: 863–869
2. Kyriazis J, Kalogeropoulou K, Bilirakis L. *et al.* Dialysate magnesium level and blood pressure. *Kidney Int* 2004; 66: 1221–1231
3. Dolson GM, Ellis KJ, Bernardo MV, Prakash R, Adroque HJ. Acute decreases in serum potassium augment blood pressure. *Am J Kidney Dis* 1995; 26: 321–326

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 cuprophane 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 activation 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.

References

1. Dinarello CA. Cytokines: agents provocateurs in hemodialysis? *Kidney Int* 1992; 41: 683–694
2. Acute intradialytic well-being: results of a clinical trial comparing polysulfone with cuprophane. Bergamo Collaborative Dialysis Study Group. *Kidney Int* 1991; 40: 714–719
3. Collins DM, Lambert MB, Tannenbaum JS, Oliverio M, Schwab SJ. Tolerance of hemodialysis: a randomized prospective trial of high-flux versus conventional high-efficiency hemodialysis. *J Am Soc Nephrol* 1993; 4: 148–154
4. Quereda C, Orofino L, Marcen R, Sabater J, Matesanz R, Ortuno J. Influence of dialysate and membrane biocompatibility on hemodynamic stability in hemodialysis. *Int J Artif Organs* 1988; 11: 259–264
5. Aakhus S, Bjoernstad K, Jorstad S. Systemic cardiovascular response in hemodialysis without and with ultrafiltration with membranes of high and low biocompatibility. *Blood Purif* 1995; 13: 229–240
6. Singh NP, Banal R, Thakur A, Kohli R, Bansal RC, Agarwal SK. Effect of membrane composition on cytokine production and clinical symptoms during hemodialysis: a crossover study. *Renal Failure* 2003; 25: 419–430
7. van Kuijk WH, Buurman WA, Gerlag PG, Leunissen KM. Vascular reactivity during combined ultrafiltration-hemodialysis: influence of dialysate-derived contaminants. *J Am Soc Nephrol* 1996; 7: 2664–2669

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 ($\geq 37^{\circ}\text{C}$), 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 $37\text{--}37.5^{\circ}$ [5,11–20]. Most studies were of relatively short duration. Only one small study compared cool dialysis with dialysate temperatures $<37^{\circ}\text{C}$. 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 $<35^{\circ}\text{C}$, the working group felt that dialysate temperatures $<35^{\circ}\text{C}$ 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 $<35^{\circ}\text{C}$.

Recommendations for research

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

References

1. Maggiore Q, Pizzarelli F, Dattolo P, Maggiore U, Cerrai T. Cardiovascular stability during haemodialysis, haemofiltration and haemodiafiltration. *Nephrol Dial Transplant* 2000; 15 [Suppl 1]: 68–73
2. van der Sande FM, Kooman JP, Konings CJ, Leunissen KM. Thermal effects and blood pressure response during postdilution hemodiafiltration and hemodialysis: the effect of amount of replacement fluid and dialysate temperature. *J Am Soc Nephrol* 2001; 12: 1916–1920
3. Rosales LM, Schneditz D, Morris AT, Rahmati S, Levin NW. Isothermic hemodialysis and ultrafiltration. *Am J Kidney Dis* 2000; 36: 353–361
4. Schneditz D, Martin K, Kramer M, Kenner T, Skrabal F. Effect of controlled extracorporeal blood cooling on ultrafiltration-induced blood volume changes during hemodialysis. *J Am Soc Nephrol* 1997; 8: 956–964
5. Maggiore Q, Pizzarelli F, Sisca S. *et al.* Blood temperature and vascular stability during hemodialysis and hemofiltration. *Trans Am Soc Artif Intern Organs* 1982; 28: 523–527
6. Maggiore Q, Enia G, Catalano C, Pizzarelli F. Studies on hemodialysis hyperthermia. *Blood Purif* 1984; 2: 125–129
7. Maggiore Q, Pizzarelli F, Sisca S, Catalano C, Delfino D. Vascular stability and heat in dialysis patients. *Contrib Nephrol* 1984; 41: 398–402
8. van der Sande FM, Rosales LM, Brenner Z *et al.* Effect of ultrafiltration on thermal variables, skin temperature, skin blood flow, and energy expenditure during ultrapure hemodialysis. *J Am Soc Nephrol* 2005; 16: 1824–1831
9. van der Sande FM, Kooman JP, Burema JH *et al.* Effect of dialysate temperature on energy balance during hemodialysis: quantification of extracorporeal energy transfer. *Am J Kidney Dis* 1999; 33: 1115–1121

10. Levy FL, Grayburn PA, Foulks CJ, Brickner ME, Henrich WL. Improved left ventricular contractility with cool temperature hemodialysis. *Kidney Int* 1992; 41: 961–965
11. van Kuijk WH, Luik AJ, de Leeuw PW. *et al.* Vascular reactivity during haemodialysis and isolated ultrafiltration: thermal influences. *Nephrol Dial Transplant* 1995; 10: 1852–1858
12. Dheenan S, Henrich WL. Preventing dialysis hypotension: a comparison of usual protective maneuvers. *Kidney Int* 2001; 59: 1175–1181
13. Marcen R, Quereda C, Orofino L. *et al.* Hemodialysis with low-temperature dialysate: a long-term experience. *Nephron* 1988; 49: 29–32
14. Orofino L, Marcen R, Quereda C *et al.* Epidemiology of symptomatic hypotension in hemodialysis: is cool dialysate beneficial for all patients? *Am J Nephrol* 1990; 10: 177–180
15. Yu AW, Ing TS, Zabaneh RI, Daugirdas JT. Effect of dialysate temperature on central hemodynamics and urea kinetics. *Kidney Int* 1995; 48: 237–243
16. Kerr PG, van Bakel C, Dawborn JK. Assessment of the symptomatic benefit of cool dialysate. *Nephron* 1989; 52: 166–169
17. Sherman RA, Rubin MP, Cody RP, Eisinger RP. Amelioration of hemodialysis-associated hypotension by the use of cool dialysate. *Am J Kidney Dis* 1985; 5: 124–127
18. Kaufman AM, Morris AT, Lavarias VA *et al.* Effects of controlled blood cooling on hemodynamic stability and urea kinetics during high-efficiency hemodialysis. *J Am Soc Nephrol* 1998; 9: 877–883
19. Jost CM, Agarwal R, Khair-el-Din T, Grayburn PA, Victor RG, Henrich WL. Effects of cooler temperature dialysate on hemodynamic stability in ‘problem’ dialysis patients. *Kidney Int* 1993; 44: 606–612
20. Quereda C, Orofino L, Marcen R, Sabater J, Matesanz R, Ortuno J. Influence of dialysate and membrane biocompatibility on hemodynamic stability in hemodialysis. *Int J Artif Organs* 1988; 11: 259–264
21. Ayoub A, Finlayson M. Effect of cool temperature dialysate on the quality and patients’ perception of haemodialysis. *Nephrol Dial Transplant* 2004; 19: 190–194
22. Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA. Midodrine and cool dialysate are effective therapies for symptomatic intradialytic hypotension. *Am J Kidney Dis* 1999; 33: 920–926
23. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. *Nephrol Dial Transplant* 2006; 21: 1883–1898
24. Fine A, Penner B. The protective effect of cool dialysate is dependent on patients’ predialysis temperature. *Am J Kidney Dis* 1996; 28: 262–265
25. Maggiore Q, Pizzarelli F, Santoro A *et al.* The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. *Am J Kidney Dis* 2002; 40: 280–290

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.

References

1. Baldamus CA, Ernst W, Frei U, Koch KM. Sympathetic and hemodynamic response to volume removal during

- different forms of renal replacement therapy. *Nephron* 1982; 31: 324–332
2. Movilli E, Camerini C, Zein H, D'Avolio G, Sandrini M, Strada A, Maiorca R. A prospective comparison of bicarbonate dialysis, hemodiafiltration, and acetate-free biofiltration in the elderly. *Am J Kidney Dis* 1996; 27: 541–547
 3. Altieri P, Sorba G, Bolasco P *et al.* Predilution haemofiltration—the Second Sardinian Multicentre Study: comparisons between haemofiltration and haemodialysis during identical Kt/V and session times in a long-term cross-over study. [see comment]. *Nephrol Dial Transplant* 2001; 16: 1207–1213
 4. Nakagawa S. Multifactorial evaluation of hemofiltration therapy in comparison with conventional hemodialysis. *Artif Organs* 1980; 4: 94–102
 5. Hampl H, Paepfer H, Unger V, Kessel MW. Hemodynamics during hemodialysis, sequential ultrafiltration and hemofiltration. *J Dial* 1979; 3: 51–71
 6. Schrandt-vd Meer AM, ter Wee PM, Kan G, Donker AJ, van Dorp WT. Improved cardiovascular variables during acetate free biofiltration. *Clin Nephrol* 1999; 51: 304–309
 7. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. *J Am Soc Nephrol* 2000; 11: 2344–2350
 8. Rabindranath KS, Strippoli GF, Roderick P, Wallace SA, Macleod AM, Daly C. Comparison of hemodialysis, hemofiltration, and acetate-free biofiltration for ESRD: systematic review. *Am J Kidney Dis* 2005; 45: 437–447
 9. Fox SD, Henderson LW. Cardiovascular response during hemodialysis and hemofiltration: thermal, membrane, and catecholamine influences. *Blood Purif* 1993; 11: 224–236
 10. Di Filippo S, Manzoni C, Andrulli S, Tentori F, Locatelli F. Sodium removal during pre-dilution haemofiltration. *Nephrol Dial Transplant* 2003; 18 [Suppl 7]: vii31–vii36
 11. Locatelli F, Di Filippo S, Manzoni C. Removal of small and middle molecules by convective techniques. *Nephrol Dial Transplant* 2000; 15 [Suppl 2]: 37–44
 12. Maggiore Q, Pizzarelli F, Sisca S, Zoccali C, Parlongo S, Nicolo F, Creazzo G. Blood temperature and vascular stability during hemodialysis and hemofiltration. *Trans Am Soc Artif Intern Organs* 1982; 28: 523–527
 13. Pizzarelli F, Sisca S, Zoccali C. *et al.* Blood temperature and cardiovascular stability in hemofiltration. *Int J Artif Organs* 1983; 6: 37–41
 14. Van Kuijk WH, Hillion D, Savoie C, Leunissen KM. Critical role of the extracorporeal blood temperature in the hemodynamic response during hemofiltration. *J Am Soc Nephrol* 1997; 8: 949–955
 15. Donauer J, Schweiger C, Rumberger B, Krumme B, Bohler J. Reduction of hypotensive side effects during online-haemodiafiltration and low temperature haemodialysis. *Nephrol Dial Transplant* 2003; 18: 1616–1622
 16. Beerenhout C, Kooman JP, Claessens P, van der Sande FM, Leunissen KM. Thermal effects of different dialysis techniques and blood pump speeds: an in vitro study. *J Nephrol* 2003; 16: 552–557
 17. Beerenhout C, Dejagere T, van der Sande FM, Bekers O, Leunissen KM, Kooman JP. Haemodynamics and electrolyte balance: a comparison between on-line pre-dilution haemofiltration and haemodialysis. *Nephrol Dial Transplant* 2004; 19: 2354–2359
 18. van der Sande FM, Kooman JP, Konings CJ, Leunissen KM. Thermal effects and blood pressure response during postdilution hemodiafiltration and hemodialysis: the effect of amount of replacement fluid and dialysate temperature. *J Am Soc Nephrol* 2001; 12: 1916–1920
 19. Karamperis N, Sloth E, Jensen JD. Predilution hemodiafiltration displays no hemodynamic advantage over low-flux hemodialysis under matched conditions. *Kidney Int* 2005; 67: 1601–1608
 20. Altieri P, Sorba G, Bolasco P *et al.* Comparison between hemofiltration and hemodiafiltration in a long-term prospective cross-over study. *J Nephrol* 2004; 17: 414–422
- **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 isovolemic 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.
- References**
1. Baldamus CA, Ernst W, Frei U, Koch KM. Sympathetic and hemodynamic response to volume removal during different forms of renal replacement therapy. *Nephron* 1982; 31: 324–332
 2. Hampl H, Paepfer H, Unger V, Kessel MW. Hemodynamics during hemodialysis, sequential ultrafiltration and hemofiltration. *J Dial* 1979; 3: 51–71
 3. Bergstrom J, Asaba H, Fuerst P, Oules R. Dialysis ultrafiltration and blood pressure. *Proc Eur Dial Transplant Assoc* 1976; 13: 293–300
 4. van der Sande FM, Gladziwa U, Kooman JP, Bocker G, Leunissen KM. Energy transfer is the single most important factor for the difference in vascular response between isolated ultrafiltration and hemodialysis. *J Am Soc Nephrol* 2000; 11: 1512–1517
 5. van Kuijk WH, Luik AJ, de Leeuw PW *et al.* Vascular reactivity during haemodialysis and isolated ultrafiltration: thermal influences. *Nephrol Dial Transplant* 1995; 10: 1852–1858
 6. Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolo F. Influence of blood temperature on vascular stability during hemodialysis and isolated ultrafiltration. *Int J Artif Organs* 1985; 8: 175–178
 7. Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolo F, Parlongo S. Effect of extracorporeal blood cooling on dialytic arterial hypotension. *Proc Eur Dial Transplant Assoc* 1981; 18: 597–602

8. Dheenan S, Henrich WL. Preventing dialysis hypotension: a comparison of usual protective maneuvers. *Kidney Int* 2001; 59: 1175–1181

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 $\pm 30\%$ less in patients with prescribed UF rates < 11 ml/kg/h compared with patients with higher prescribed 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

1. Brunet P, Saingra Y, Leonetti F, Vacher-Coponat H, Ramananarivo P, Berland Y. Tolerance of haemodialysis: a randomized cross-over trial of 5-h versus 4-h treatment time. *Nephrol Dial Transplant* 1996; 11 [Suppl 8]: 46–51
2. van der Sande FM, Mulder AW, Hoorntje SJ *et al.* The hemodynamic effect of different ultrafiltration rates in patients with cardiac failure and patients without cardiac failure: comparison between isolated ultrafiltration and ultrafiltration with dialysis. *Clin Nephrol* 1998; 50: 301–308
3. Saran R, Bragg-Gresham JL, Levin NW *et al.* Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int* 2006; 69: 1222–1228
4. Charra B. Control of blood pressure in long slow hemodialysis. *Blood Purif* 1994; 12: 252–258
5. Fagugli RM, Reboldi G, Quintaliani G *et al.* Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis* 2001; 38: 371–376
6. Andre MB, Rebold SM, Pereira CM, Lugon JR. Prospective evaluation of an in-center daily hemodialysis program: results of two years of treatment. *Am J Nephrol* 2002; 22: 473–479
7. Okada K, Abe M, Hagi C *et al.* Prolonged Protective Effect of Short Daily Hemodialysis against Dialysis-Induced Hypotension. *Kidney Blood Press Res* 2005; 28: 68–76
8. Heidenheim AP, Muirhead N, Moist L, Lindsay RM. Patient quality of life on quotidian hemodialysis. *Am J Kidney Dis* 2003; 42 [1 Suppl]: 36–41

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 interdialytic BP control. Assess the effect of different dosing schedules on the same parameters.

References

1. Charra B. Control of blood pressure in long slow hemodialysis. *Blood Purif* 1994; 12: 252–258

2. Ozkahya M, Ok E, Cirit M *et al*. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant* 1998; 13: 1489–1493
3. Tisler A, Akocsi K, Harshegyi I *et al*. Comparison of dialysis and clinical characteristics of patients with frequent and occasional hemodialysis-associated hypotension. *Kidney Blood Press R* 2002; 25: 97–102
4. Sherman RA, Casale P, Cody R, Horton MW. Effect of predialysis verapamil on intradialytic blood pressure in chronic hemodialysis patients. *ASAIO Transactions* 1990; 36: 67–69
5. Man in 't Veld AJ, Schicht IM, Derkx FH, de Bruyn JH, Schalekamp MA. Effects of an angiotensin-converting enzyme inhibitor (captopril) on blood pressure in anephric subjects. *Br Med J* 1980; 280: 288–290

- **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 paresthesias, 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 sertraline, 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

1. Prakash S, Garg AX, Heidenheim AP, House AA. Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. *Nephrol Dial Transplant* 2004; 19: 2553–2558
2. Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA. Midodrine and cool dialysate are effective therapies for symptomatic intradialytic hypotension. *Am J Kidney Dis* 1999; 33: 920–926
3. Lindberg JS, Copley JB, Melton K, Wade CE, Abrams J, Goode D. Lysine vasopressin in the treatment of refractory hemodialysis-induced hypotension. *Am J Nephrol* 1990; 10: 269–275
4. Milutinovic S. Dihydroergotamine in the treatment of patients with symptomatic hypotension during regular hemodialysis. *Arzneimittel-Forschung* 1987; 37: 554–556
5. Peer G, Itzhakov E, Wollman Y *et al.* Methylene blue, a nitric oxide inhibitor, prevents haemodialysis hypotension. *Nephrol Dial Transplant* 2001; 16: 1436–1441
6. Iida N, Tsubakihara Y, Shirai D, Imada A, Suzuki M. Treatment of dialysis-induced hypotension with L-threo-3,4-dihydroxyphenylserine. *Nephrol Dial Transplant* 1994; 9: 1130–1135
7. Anand U, Bastani B, Dhanraj P, Ballal SH. Intradialytic dobutamine therapy in maintenance hemodialysis patients with persistent hypotension. *Am J Nephrol* 1999; 19: 459–463
8. Brewster UC, Ciampi MA, bu-Alfa AK, Perazella MA. Addition of sertraline to other therapies to reduce dialysis-associated hypotension. *Nephrol (Carlton)* 2003; 8: 296–301
9. Yalcin AU, Sahin G, Erol M, Bal C. Sertraline hydrochloride treatment for patients with hemodialysis hypotension. *Blood Purif* 2002; 20: 150–153
10. van der Zee S, Thompson A, Zimmerman R *et al.* Vasopressin administration facilitates fluid removal during hemodialysis. *Kidney Int* 2007; 71: 318–324

- **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 considered. 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

1. van Es A, Henny FC, Kooistra MP, Lobatto S, Scholte HR. Amelioration of cardiac function by L-carnitine administration in patients on haemodialysis. *Contrib Nephrol* 1992; 98: 28–35
2. Riley S, Rutherford S, Rutherford PA. Low carnitine levels in hemodialysis patients: relationship with functional activity status and intra-dialytic hypotension. *Clin Nephrol* 1997; 48: 392–393
3. Ahmad S, Robertson HT, Golper TA, *et al.* Multicenter trial of L-carnitine in maintenance hemodialysis patients. II. Clinical and biochemical effects. *Kidney Int* 1990; 38: 912–8
4. Eknoyan G, Latos DL, Lindberg J. National Kidney Foundation Carnitine Consensus Conference. Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder. National Kidney Foundation Carnitine Consensus Conference. *Am J Kidney Dis* 2003; 41: 868–876

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 manoeuvre, 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 manoeuvre for IDH.

1. Bivins HG, Knopp R, dos Santos PA. Blood volume distribution in the Trendelenburg position. *Ann Emerg Med* 1985; 14: 641–643
2. Sibbald WJ, Paterson NA, Holliday RL, Baskerville J. The Trendelenburg position: hemodynamic effects in hypotensive and normotensive patients. *Crit Care Med* 1979; 7: 218–224
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 manoeuvre 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 manoeuvre 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 manoeuvre 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 in 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, hypertonically 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-ethylstarch (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.

1. Nette RW, Krepel HP, van den Meiracker AH, Weimar W, Zietse R. Specific effect of the infusion of glucose on blood volume during haemodialysis. *Nephrol Dial Transplant* 2002; 17: 1275–1280
2. 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
3. van der Sande FM, Kooman JP, Barendregt JN, Nieman FH, Leunissen KM. Effect of intravenous saline, albumin, or

- hydroxyethylstarch on blood volume during combined ultrafiltration and hemodialysis. *J Am Soc Nephrol* 1999; 10: 1303–1308
4. Knoll GA, Grabowski JA, Dervin GF, O'Rourke K. A randomized, controlled trial of albumin versus saline for the treatment of intradialytic hypotension. *J Am Soc Nephrol* 2004; 15: 487–492
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 IDH 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.

Reference

1. Maggiore Q, Pizzarelli F, Santoro A *et al.* The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. [see comments.]. *Am J Kidney Dis* 2002; 40: 280–290