Hemodynamic stability during hemodialysis
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 8

Summary, general discussion and future perspectives
Summary

Despite technological advances in hemodialysis treatment, intradialytic hypotension (IDH) remains an important hazard of dialysis treatment. Several factors could contribute to the onset of IDH, including inadequate cardiovascular compensation of the ultrafiltration-induced hypovolemia\(^1\)-\(^3\), autonomic dysfunction\(^4\)-\(^7\), dialysis-induced excessive nitric oxide (NO) production\(^6\),\(^8\)-\(^13\) and relative vasopressin deficiency\(^10\),\(^13\)-\(^17\). The biofeedback system Hemocontrol, characterized by an initially higher dialysate sodium concentration and ultrafiltration rate, is associated with improved intradialytic hemodynamic stability\(^18\)-\(^21\). The mechanism behind this improved hemodynamic stability has not been fully elucidated. Hemocontrol is designed to preserve blood volume during hemodialysis. In practice, however, the intradialytic blood volume course does not differ substantially from conventional hemodialysis. Therefore, presumably other factors contribute to the improved intradialytic hemodynamic stability with Hemocontrol. The transient increase in plasma sodium levels induced by Hemocontrol could result in osmotic vasopressin release and could affect sympathetic activity and endothelial function.

To address the potential role of vasopressin in the pathophysiology of IDH, we performed a systematic literature review and meta-analysis in chapter 2. We specifically studied the course of vasopressin levels during conventional hemodialysis and other techniques like ultrafiltration- and sodium profiling and in relation to IDH. Although predialysis plasma vasopressin levels were significantly higher in dialysis patients compared to healthy individuals, vasopressin levels showed little or no change during conventional hemodialysis. Regarding the potential association between vasopressin deficiency and IDH, inconsistent findings were obtained. Only few studies were performed, some reporting higher vasopressin levels following an episode of IDH\(^22\),\(^24\), whereas in others no such association was found\(^25\),\(^26\).

Next, to study whether modification of the dialysate sodium concentration, and consequently, plasma sodium levels have an effect on plasma vasopressin levels, we performed a randomized study comparing intradialytic plasma vasopressin levels during conventional hemodialysis and Hemocontrol dialysis in chapter 3. Plasma vasopressin levels did not change during conventional hemodialysis, in line with findings from the systematic literature review. In contrast, plasma vasopressin levels were significantly higher during the first hour of dialysis with Hemocontrol compared to standard hemodialysis. We hypothesized that vasopressin-induced vasoconstriction during Hemocontrol dialysis permitted initially higher ultrafiltration volumes, facilitating improved hemodynamic stability during the second half of treatment. Alternatively, the higher plasma sodium levels might affect endothelial function and lower the production rate of the vasodilator NO and/or could enhance the activity of the sympathetic nervous system. To investigate these hypotheses, we expanded
the comparison between standard hemodialysis and Hemocontrol dialysis in another, larger, cohort of patients described in chapter 4. We confirmed our previous finding that plasma vasopressin levels were initially higher during Hemocontrol dialysis compared with standard hemodialysis. Also, the overall blood pressure was higher with Hemocontrol dialysis and there was an association between the intradialytic course of vasopressin and mean arterial pressure. The transient plasma sodium peak during Hemocontrol dialysis was not associated with a different course of endothelial function markers or enhanced sympathetic nervous system compared with standard hemodialysis. Thus, no evidence for a down-regulating effect of a transient intradialytic increase in plasma sodium concentration on endothelial function nor a stimulating effect on sympathetic nervous system activity was found in this cohort of prevalent hemodialysis patients.

Since both the systematic review and the studies described in chapter 3 and 4 showed that vasopressin levels hardly rose during conventional hemodialysis, we questioned whether the established stimuli for vasopressin release, hypovolemia and hypotension, are operative in dialysis patients. To this end, we related the intradialytic course of plasma sodium, blood pressure and blood volume to repeatedly measured copeptin levels in a cohort of 108 patients in chapter 5. We studied copeptin since vasopressin measurements were not available in this patient cohort. Copeptin is a part of the vasopressin precursor with unknown physiological function and is claimed to be a surrogate marker for vasopressin27. Predialysis plasma copeptin levels were markedly elevated compared to the reference value for healthy subjects. Copeptin levels rose during conventional hemodialysis and the intradialytic rise in copeptin was associated with decreases in blood pressure and blood volume. There was no significant association between the course of copeptin and the intradialytic change in plasma sodium concentration, which is presumably explained by the small intradialytic change in sodium concentration of less than 1 mmol/L in this study.

Copeptin is increasingly used as a marker for vasopressin in several research fields including patients with chronic kidney disease (CKD)28, because vasopressin measurement is allegedly affected by pre-analytical variation due to adherence to platelets and limited ex vivo stability of vasopressin compared to copeptin29-31. However, no direct comparison of effects of pre-analytical variability on vasopressin and copeptin concentration has been made so far. Therefore, we studied the effects of several pre-analytical processing conditions on vasopressin and copeptin concentration in chapter 6, and found that copeptin, in contrast to vasopressin, was not susceptible to pre-analytical sample handling. Copeptin concentration was unaffected by centrifugation force, delayed processing and repeated freezing and thawing, whereas vasopressin concentration was affected by all these conditions. On the other hand, storage temperature and storage duration for at least four months at -80°C or -150°C did not influence both vasopressin and copeptin levels.

When using copeptin as a surrogate marker for vasopressin in patients with chronic
kidney disease (CKD), it is essential to know whether renal function affects copeptin and vasopressin concentrations and if the copeptin and vasopressin ratio is constant when renal function declines. Importantly, hemodialysis treatment could also induce a disparity between the intradialytic course of copeptin and vasopressin as a result of a difference in dialyzability due to a difference in molecular weight or binding to platelets\textsuperscript{29,32-34}. Therefore, vasopressin and copeptin levels were studied in healthy individuals and in patients with CKD, including hemodialysis patients, in chapter 7. Both copeptin and vasopressin levels gradually rose with decreasing renal function and plasma copeptin and vasopressin levels were significantly higher in dialysis patients compared to non-dialysis patients. The copeptin/vasopressin ratio remained constant in the range of renal function above 30 ml/min/1.73m\textsuperscript{2}, whereas it increased in patients with an eGFR below 30 ml/min/1.73m\textsuperscript{2}, indicating that copeptin levels increased to a greater extent than vasopressin levels. In hemodialysis patients, the copeptin/vasopressin ratio was higher compared to non-dialysis patients with CKD and healthy individuals and increased further during hemodialysis. The clearance rate of vasopressin by hemodialysis was higher than that of copeptin.

**General discussion and future perspectives**

**Plasma vasopressin and copeptin levels during conventional hemodialysis**

From the systematic literature review and chapters 3 and 4 it is apparent that plasma vasopressin levels show little or no change during conventional hemodialysis, despite removal of a large fluid volume in a relatively short period of time\textsuperscript{2}. The inevitable decrease in blood volume and often also blood pressure that occur during hemodialysis with ultrafiltration are physiological stimuli for vasopressin release\textsuperscript{35}. At the same time, the fall in plasma osmolality that can occur during conventional hemodialysis as shown in chapter 2 can counteract vasopressin release. Although hyperosmolality counts as the primary stimulus for vasopressin release\textsuperscript{36}, it is widely accepted that hypovolemia overrides osmoreceptor-induced inhibition of vasopressin release in case of volume depletion\textsuperscript{35,37}. This phenomenon is named “the law of the circulating volume”\textsuperscript{38}.

In chapter 5 we found an increase in plasma copeptin levels during conventional hemodialysis. This observation contrasts with the observed decrease in intradialytic vasopressin concentration, since copeptin is allegedly produced and secreted into the circulation in equimolar amounts with vasopressin\textsuperscript{29,31,33}. Thus, vasopressin concentration hardly increases during conventional hemodialysis as shown in chapter 2, 3 and 4, whereas copeptin levels did increase as shown in chapter 5. A plausible explanation for this observed difference is a disparity in the dialyzability of both molecules. Vasopressin is much smaller (molecular size of about 1 kDa)\textsuperscript{34,35} than copeptin (molecular size of about 5 kDa)\textsuperscript{29} and is, therefore, more likely to be cleared by hemodialysis. This was indeed shown in chapter
7. Alternative explanations for the lack of a rise in vasopressin levels during conventional hemodialysis have been proposed in literature. First, an ultrafiltration-induced hypovolemic stimulus might not be sufficient to stimulate vasopressin release\textsuperscript{13,34}. Second, insensitivity of the hypothalamic-pituitary interaction as a result of uremia could hamper vasopressin release\textsuperscript{39}. Copeptin was used as a surrogate marker for vasopressin in chapter 5 but from our findings in chapter 7 it shows that copeptin does not exactly reflect the vasopressin concentration during hemodialysis. It is assumed that vasopressin and copeptin are released together from the pituitary gland upon stimuli after cleavage of the precursor hormone preprovasopressin\textsuperscript{40,41}. Thus, the intradialytic increase in copeptin observed in chapter 4 and 5 presumably indicates that vasopressin release during conventional hemodialysis is present. The intradialytic increase in copeptin was associated with a decrease in blood pressure and blood volume in chapter 5. Thus, the alternative explanations for the lack of an increase in intradialytic vasopressin levels, i.e. hemodialysis providing an insufficient stimulus for vasopressin release or insensitivity of the hypothalamic-pituitary interaction, seem unlikely based on the observations in chapter 5. Incomplete removal of copeptin during hemodialysis might result in gradual accumulation over time, provided that the in vivo copeptin half-life is long enough. Gradual accumulation might account for the high pre-treatment copeptin levels observed in chapters 5 and 7 and previous studies\textsuperscript{42,43}. Although we did not find an association between dialysis vintage and predialysis copeptin levels in chapter 5 and 7, such a relation was reported in two previous studies\textsuperscript{42,43} supporting the theory of copeptin accumulation in hemodialysis patients.

Recently, it has been postulated that copeptin levels may have prognostic value in renal and cardiovascular disease\textsuperscript{28,44}. In hemodialysis patients with type 2 diabetes, higher predialysis copeptin levels were associated with a higher incidence of cardiovascular events, sudden death and all-cause mortality\textsuperscript{42}. It is unclear if copeptin has a causative role in the pathophysiology of renal and cardiovascular disease or is just a marker\textsuperscript{44}. Hemodialysis treatments in which high ultrafiltration rates were used and large decreases in blood pressure were observed were also associated with a higher incidence of cardiovascular events and all-cause mortality\textsuperscript{45-47}. Particularly dialysis treatments with such great volume shifts probably lead to increases in plasma copeptin levels given our results in chapter 5.

**Effect of sodium modification on vasopressin levels; the Hemocontrol system unraveled?**

Plasma vasopressin release during hemodialysis can be stimulated using the Hemocontrol biofeedback system during hemodialysis, as shown in chapter 3 and 4. Hemocontrol dialysis induces a volumetric stimulus by using an initially higher ultrafiltration rate and also an osmotic stimulus especially early during dialysis by modification of the dialysate sodium concentration. Thus, a ‘double’ stimulus for vasopressin release during hemodialysis is provided, in contrast to conventional hemodialysis. Hemocontrol dialysis is associated with
improved intradialytic hemodynamic stability compared to conventional hemodialysis\textsuperscript{18,20,21,48}. The Hemocontrol system is originally designed to preserve blood volume during hemodialysis and the general believe is that initially higher plasma sodium levels, which are the result of Hemocontrol, increase plasma refilling from the interstitial tissue\textsuperscript{1,16,49,50}. Previous studies, however, did not show better blood volume preservation compared with conventional hemodialysis\textsuperscript{21,51}. In the literature, mixed effects of the dialysate sodium concentration on plasma refill rate are described. Some groups found an increase in plasma refill rate when dialysate sodium concentration was temporarily increased\textsuperscript{51-53}, whereas in other studies no significant increase in plasma refill in response to higher dialysate sodium levels was observed\textsuperscript{54,55}. We found that plasma refill rate was comparable for standard hemodialysis and Hemocontrol hemodialysis in chapters 3 and 4, despite the higher plasma sodium levels with Hemocontrol during the first half of treatment. The sensitivity of methods used to measure vascular refilling and/or differences in achieved plasma sodium levels may account for the observed differences between studies. Taken together, the mechanism leading to improved hemodynamic stability with Hemocontrol is not easily explained by an effect on blood volume. The studies described in chapters 3 and 4 suggest that higher Hemocontrol-induced vasopressin levels could be a good ‘candidate’ to explain the improved intradialytic hemodynamic stability, at least in part. A role for vasopressin in maintaining hemodynamic stability during hemodialysis has been proposed before\textsuperscript{13,16,56}. In line with this reasoning, Shimizu \textit{et al} found that infusion of hypertonic saline resulted in a rise in blood pressure by stimulating vasopressin release without a concomitant increase in plasma volume\textsuperscript{57,58}. Alternatively, a rise in plasma sodium concentration may affect endothelial function and sympathetic nervous system activity, which could also contribute to improved hemodynamic stability with Hemocontrol dialysis. However, a similar course of various plasma indices of endothelial function during standard hemodialysis and Hemocontrol hemodialysis was found. Our findings were in agreement with one previous study in which no difference in nitrite and endothelin-1 levels as measures of endothelial function between hemodialysis with low and high dialysate sodium levels was found\textsuperscript{59}. We also did not find an effect of a transient increase in plasma sodium concentration on several markers of sympathetic activity during Hemocontrol dialysis compared with standard hemodialysis. This is also in line with other studies, showing that hemodialysis with sodium profiling was not associated with higher heart rate variability indices based on the interbeat intervals\textsuperscript{60}, baroreflex sensitivity\textsuperscript{61} or plasma norepinephrine levels\textsuperscript{62}.

**Copeptin as marker for vasopressin**

In the past decade, copeptin is frequently used as a marker for vasopressin in several patient populations\textsuperscript{27,28}. Strong correlations between copeptin and vasopressin have been reported\textsuperscript{29,30,63-66}, but no studies in hemodialysis patients were performed. Because
of the observed differences between intradialytic levels of vasopressin and copeptin in chapters 3, 4 and 5, the question rose whether copeptin is a good and suitable substitute for vasopressin in hemodialysis patients. Indeed, the copeptin/vasopressin ratio increased during hemodialysis, which could, at least partially, be explained by a greater clearance rate of vasopressin compared to copeptin. Thus, the intradialytic copeptin concentration does not provide an accurate reflection of the vasopressin concentration. Interestingly, a divergent course between copeptin and vasopressin was already observed in CKD patients not on dialysis with an eGFR of 28 ml/min/1.73m² and below. In these patients, copeptin levels increased to a greater extent relative to vasopressin when renal function was 28 ml/min/1.73m² and below, whereas the copeptin/vasopressin ratio remained constant at an eGFR above 28 ml/min/1.73m². The reason why copeptin levels increased to a greater extent than vasopressin levels when renal function is severely impaired is not completely understood. Since copeptin was found to be present in urine, a renal component is presumably part of the copeptin clearance. On the other hand, a rapid decline in copeptin levels upon water loading suggests a non-renal, faster copeptin clearance mechanism. Possibly also an increased clearance of vasopressin could explain the increased copeptin/vasopressin ratio observed in patients with severely impaired kidney function.

Potential of vasopressin administration in the prevention of dialysis hypotension?
The results from this thesis suggest that vasopressin-induced vasoconstriction could contribute to better intradialytic hemodynamic stability. Therapeutic administration of vasopressin or one of its analogues has been studied in the past, as discussed in chapter 2, but data are scarce. Intravenous vasopressin administration was associated with a more stable and higher blood pressure and with a lower incidence of IDH compared with placebo, but these were all small studies up to 22 patients.

In the intensive care setting, vasopressin has been investigated more thoroughly. Administration of vasopressin has been shown to support blood pressure in patients with several shock states and infusion of vasopressin (up to 0.03 U/min) can be used in addition to noradrenalin infusion to increase MAP or to decrease used catecholamine dosages as proposed in the International Guidelines for Management of Severe Sepsis and Septic Shock. Supplementary use of vasopressin in catecholamine-resistant vasodilatory shock due to calcium channel antagonist intoxication has also been proposed. Exogenous vasopressin can have adverse effects like enhanced platelet aggregation, myocardial and mesenteric ischemia and ischemic skin lesions but the risk of adverse effects seems to be limited when vasopressin is administered at a dose <0.04 U/min. Besides vasopressin, terlipressin has been shown to support blood pressure in patients with shock and hepatorenal syndrome. Terlipressin is a synthetic analogue of vasopressin with a similar molecular weight as vasopressin of approximately 1 kDa and is converted into lysine.
vasopressin. Terlipressin has a greater affinity for vascular V1 receptors than vasopressin\textsuperscript{35} and its vasopressor effect lasts approximately five to eight hours\textsuperscript{35,93,94}. In that perspective, terlipressin would be more suitable for maintaining hemodynamic stability during hemodialysis than vasopressin or the other vasopressin analogue desmopressin, which mainly acts on V2 receptors and has less vasoconstrictive effects\textsuperscript{85}. Although small studies showed promising results, large randomized-controlled trials are needed to establish the efficacy of vasopressin and/or terlipressin in reducing dialysis hypotension and to determine the optimal dosage, timing of administration and safety profile of both drugs.

**Key messages**

In CKD patients not on dialysis with an eGFR above 28 ml/min/1.73m\textsuperscript{2}, the ratio of copeptin and vasopressin remained constant whereas in patients with an eGFR of 28 ml/min/1.73m\textsuperscript{2} and below, vasopressin and copeptin levels diverged with higher copeptin relative to vasopressin levels. In hemodialysis patients, copeptin did not reflect the vasopressin concentration, at least partly due to a greater clearance rate by hemodialysis of vasopressin compared to copeptin. During conventional hemodialysis, vasopressin levels did not increase, most likely due to clearance by hemodialysis. Modification of the dialysate sodium concentration by the Hemocontrol biofeedback system combined with a more pronounced decrease in blood volume resulted in slightly but significantly higher intradialytic plasma vasopressin levels and was associated with better hemodynamic stability during treatment compared to conventional hemodialysis. Down-regulation of nitric oxide production, enhanced sympathetic activity or a higher plasma refill rate did not seem to explain the improved intradialytic hemodynamic stability with Hemocontrol dialysis. Vasopressin appears to be a promising drug to maintain intradialytic hemodynamic stability and deserves further attention.
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General discussion and future perspectives