

Summary of the EDTNA/ERCA Journal Club discussion: Autumn 2004

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The paper selected for discussion by the EDTNA/ERCA Journal Club in November 2004 was 'Haemodynamics and electrolyte balance: a comparison between on-line pre-dilution haemofiltration and haemodialysis' (1). The authors are based at the Department of Internal Medicine and Clinical Chemistry in University Hospital Maastricht, The Netherlands and the corresponding author, Dr Jeroen Kooman, kindly agreed to take part in the discussion and respond to any queries raised.

Synopsis of the discussion paper

The discussion paper can be downloaded in full from the EDTNA/ERCA website (see ref. 1). The authors of this paper wanted to see if the improved haemodynamic stability reported with haemofiltration (HF) compared to haemodialysis (HD) is mainly due to a cooling effect or to better clearance of vasodepressor substances. As changes in sodium, potassium and calcium could also influence the haemodynamics, they also wanted to compare electrolyte balance in HF and HD because it has been suggested that adhesion of negatively charged proteins to the filter membrane in HF could reduce the transport of positively charged ions.

In their study, 11 stable patients received three different treatments, in random order, on the same weekday over a three week period. The treatments were on-line pre-dilution HF with thrice-filtered infusate at 36.5°C and HD with ultrapure dialysate at 36.5 and 35.5°C. The HF sessions were carried out over the same treatment time as the HD sessions (about 4 hours) and with a very high target infusate volume of 1.2 times body weight to give small molecule clearances comparable with HD. The mean volume achieved was 75±9 litres.

For the haemodynamics, the authors measured cardiac output (CO), central blood volume (CBV) and peripheral vascular resistance (PVR, calculated as mean arterial pressure divided by CO) at the start, middle and end of each treatment using the saline dilution technique (2). Change in relative blood volume (RBV) was measured with the Gambro blood volume sensor (BVS), blood pressure was measured manually and body temperature was measured with an ear thermometer.

For the solute balance, the mass of sodium, potassium, calcium and phosphate transferred to or from the patient during treatment was determined using total dialysate or filtrate collections. The electrolyte concentrations were measured by indirect ionometry. A new parameter 'conductivity balance' was also measured to give an alternative assessment of sodium balance.

The results were rather inconclusive. The only parameters measured for which there was a significant difference between the treatments were relative and central blood volume. RBV

decreased by 9.7% in HF, 8.0% in HD36.5 and 7.7% in HD35.5 while CBV decreased by 0.16 l in HF, 0.11 l in HD36.5 and 0.03 l in HD35.5.

CO and BP tended to fall, and PVR tended to rise, during all treatments, but the change was only significant for CO in HF and there was no significant difference between the treatments. Body temperature increased by 0.3°C in HD36.5, 0.1°C in HF and 0.0°C in HD35.5, but the difference between treatments was not significant.

There was also no difference in the measured losses of sodium, potassium and phosphate, or in the change in calcium (Ca) (some patients gained Ca from the dialysate) for HF or HD.

The authors concluded that changes in haemodynamic variables in this study appear to depend more on the rate of fluid removal than the treatment modality, and that removal of electrolytes is not impaired during on-line HF.

Selected issues from the discussion

The main themes of the discussion were the problems relating to accurate measurement of electrolyte balance and the physiological significance of thermal balance. Other issues, including the quality of the dialysate and infusate, the use of manual or automated blood pressure measurements and use of in-series dialysers, that came up in the discussion in a limited way are not covered here but they have been logged as items of potential interest for future discussions.

For a review of thermal balance and electrolyte balance (up to 2002) please refer to the chapter by Polaschegg HD et al on haemodialysis machines and monitors in 'Replacement of Renal Function by Dialysis' (3).

Physiological effects of thermal energy transfer during treatment

The lack of a significant effect of low temperature dialysate on peripheral vascular resistance and blood pressure was surprising. Hans Polaschegg noted that the hypothesis that thermal balance affects blood pressure stabilisation dates back to at least Maggoire et al in 1981 (4). Dr Polaschegg had this, and the basic physiology of body temperature regulation from textbooks such as Guyton, in mind when he developed the specification for the blood temperature monitor that is now marketed by Fresenius (5). After almost 20 years, Maggiore's team demonstrated that active control of body temperature could give a significant improvement in interdialytic intolerance in patients prone to hypertension in a randomised trial (6).

Dr Polaschegg pointed out that the only reference the authors used to suggest that the cooling effect of HF is not responsible for increased haemodynamic stability, the 'Second Sardinian Multicentre Study' (ref. 4 in the paper), is poorly designed as it did not take into account cooling over the extracorporeal circuit that occurs during convective techniques.

Dr Kooman replied that his group had commented on the methods used in this study at the time in a letter to the journal editor (7). In their letter, they described one of their earlier studies in which the HF infusate had to be warmed to 39°C in order to achieve the same thermal energy balance as HD treatment with a dialysate temperature of 37.5°C (8). Despite reservations about the Sardinian Study, the authors felt the thermal effects of on-line filtration techniques merited further investigation.

Both Dr Polaschegg and Franta Lopot were critical of the use of a constant dialysate temperature for all patients. As this approach does not take patient pre-dialysis temperature variations into account, it will result in large intra-patient and inter-patient energy balance differences. Prof Lopot explained that it is generally believed that the dialysis population is hypothermic, but there is little or nothing in the literature to properly quantify this. It should be easy to do this but the old practice of taking patients' pre-HD temperature has been inexplicably abandoned.

Simply looking at the effect of temperature was missing the point, said Hans Polaschegg. It is thermal energy transfer not temperature that is the important parameter. Dialysis can be used to warm up hypothermic patients (9), he explained. If you fall into an ice-pond or are covered by snow in an avalanche and have the good luck to freeze before your brain is damaged from lack of oxygen you may recover without brain damage after rewarming.

In routine dialysis, patients come in with different temperatures and body weights, and they have different blood flows. All of these parameters will affect the thermal energy transfer. Treating everybody with the same dialysis fluid temperature will have different effects, with temperature stabilisation in some, but too much cooling or heating in others.

Franta Lopot agreed that the relation between blood flow and thermal energy transfer in the extracorporeal circuit should be studied. His group did just a few measurements and found the equation devised by Morris seemed to work (10).

Another reason for the lack of a significant effect of temperature may have been the small number of patients who completed the study (only 11) and the inclusion of only stable patients with no diabetes and no congestive or coronary heart failure. These very stable patients would be the least likely to benefit from an intervention that might be expected to help maintain haemodynamic stability. The authors' commented on this drawback of their study in the paper, saying that the study design was not suitable for monitoring hypotensive episodes (that would require several sessions on each treatment). They also noted that changes in PVR assessed by the saline dilution appears to be unable to detect changes that do give significant changes in skin blood flow (measured with laser Doppler flowmetry).

Jean-Yves De Vos informed the group that the latest Belgian Practice Registration (11) showed that the use of low temperature fluid is becoming more and more popular. A small e-survey of eleven units in Northern, Southern and Eastern Europe during the discussion showed a range of approaches to the use of low temperature dialysate. If 'low temperature' is defined as below 36.5°C, then two units used only low temperature (35 or 36°) and two used only standard temperature (36.5 or 37°). The other seven units used a standard temperature but reduced it for specific circumstances, such as fever or severe hypotension, or specific patients, such as those with cardiac problems who need high UF rates.

Noting the lack of any difference in PVR between cool and standard dialysis in this study, Jean-Yves De Vos asked if there was hard proof for the use of low temperature dialysate or if it was just a flashy trend. Dr Kooman replied that he believes that there is now ample evidence to support its use. He referred to the randomised controlled trial by Maggiore et al (6) and also the recent review by Schneditz et al (12).

Hans Polaschegg also replied to Jean-Yves, reminding the group of the physics and physiology of thermal control. Resting energy expenditure is approximately 70W (the power of a light bulb). This energy, which is completely converted into heat, is mainly dissipated

through the skin. The rate of energy loss from the body depends on the temperature gradient between skin and environment. Tests have shown that a naked person at rest in a room without draughts will feel comfortable between 33 and 36°C air temperature. At 33°C the blood flow to the skin will be minimised, at 36°C it will be maximised. So the thermal resistance between the core of the body and the environment is controlled by blood perfusion through the peripheral blood vessels.

In dialysis, volume depletion due to ultrafiltration causes the peripheral blood vessels that control heat loss to constrict. This helps to maintain CBV, but causes the body to heat up. When the body warms up by just a few tenths of a degree above the set core temperature, the peripheral circulation is forcefully opened by the thermal control process. This process is more powerful than the mechanism that tries to stabilise blood pressure during volume depletion, though interestingly both control centres are in the same region of the brain (the hypothalamus).

The effect of this competition on peripheral resistance will depend on the patient's initial vasoconstriction or vasodilation and their individual internal control set point and resting energy expenditure. Indeed, concluded Dr Polaschegg, haemodialysis could provide a wonderful opportunity to study thermal control as, so far, most studies have been done by inducing heat through heavy exercise. Such studies would be much more fruitful than endless repetition of HD versus HF, or variations of dialysate temperature.

Measurement of sodium balance

The authors of the discussion paper were looking for differences in the removal of sodium and other electrolytes with HD and HF to see if adhesion of proteins to the filter membrane in HF was inhibiting the flow of positively charged ions out of the blood. In the abstract of the paper this is described as 'an effect on the Donnan equilibrium' though it may not be appropriate to describe filtration in terms of an equilibrium.

Hans Polaschegg provided some background information, explaining that differences between HD and HF, where the fresh dialysate and infusate have identical composition (which is usually the case with on-line produced substitution fluid) are thought to emerge from different dynamics of the Gibbs-Donnan effect (13). This effect is described in every textbook on physiology, at least qualitatively. As always, said Dr Polaschegg, the original work is easier to understand than later versions.

The question of differences between filtration and diffusion Donnan equilibria has been studied by many authors over the last forty years (14-17). The results reported in these papers are in controversy, which may be the consequence of different protein gradients at the membrane but also may be the consequence of different analytical methods (flame photometry, ionometry). It would be of great interest to review these papers in detail and to measure the effects under various operating conditions.

In the discussion paper, the authors compared the amount of sodium removed from the patient by measuring the difference in the mass of sodium in the fresh and spent dialysate in HD, and in the infusate and filtrate in HF. The method they used for measuring sodium was 'indirect ionometry' which means that the fluid was diluted before the amount of sodium was measured.

For plasma, the use of indirect measurements gives a systematic error because the plasma is made up of plasma water (which contains the ionised sodium) and proteins and lipids, which add to the volume. The physiologically important sodium concentration is the plasma water level not the total plasma level. The more protein and lipid there is in the sample, the lower the total plasma level will be. When the sample is diluted before measuring the sodium, the information on the amount of protein and lipid in it is lost.

Hans Polaschegg explained that clinicians prefer to use indirect ionometry because they are used to this error. However it could be dangerous as in patients with high plasma lipid or protein concentration. The dilutional error leads to falsely low sodium reading (this is called 'pseudohyponatremia').

In the paper, the authors state that 'in contrast to direct ionometry, indirect ionometry does not need a correction factor when assessing sodium in aqueous media and yield results comparable to flame photometry'. Several contributors found this rather misleading. As Dr Polaschegg said, all the measurements for this study were in aqueous fluid so the analytical method has negligible influence on the result. For measurements such as plasma to dialysate concentration gradients, it is crucial to make the right corrections for protein and lipids to indirect methods (including flame photometry). Jeroen Kooman explained that his concerns related to direct ionometry devices that apply standard corrections to make the results comparable with flame photometry. As aqueous solutions should not have any dilution corrections, this would lead to erroneous results.

Stanley Shaldon was concerned that the reference (ref 13 in the discussion paper) used to justify the preference for using indirect ionometry was a rather obscure paper that compared methods for measuring sodium in Llamas' urine which presumably does not contain protein. Dr Kooman replied that there were surprisingly few papers on the technology for sodium measurements and the advantage of looking at llamas is that urine samples in these animals encompass a wide range of electrolyte concentrations. He referred the group to a new study by Locatelli's group in Lecco, Italy (18), which compared measurements of sodium levels in plasma and peritoneal dialysis fluid using flame photometry, direct and indirect ionometry. The authors of this paper explain the difference in the measurement using the effects of complexing with anions, dilution and pH on the ionisation (activity) of sodium and conclude that indirect ionometry can replace flame photometry in evaluating D/P_{Na} and sodium removal in PD. D/P_{Na} , The ratio of sodium in the dialysate and plasma after a specified dwell time, is used to study the transport of water across the peritoneal membrane.

Prof Shaldon has been interested in sodium fluxes for many years. He studied sodium balance in HD and HF in the 1980's and concluded that there was no evidence then for sodium retention in HF (9). He expressed his doubts about the accuracy of sodium balance measurements in general, as the method used must be calibrated using appropriate standards prepared in the measuring laboratory with obsessive gravimetric preparation methods and the samples must be carefully diluted to respect the limits that permit a linear calibration. Conductivity or ion selective electrodes have to be validated against an accepted method (flame or atomic spectrophotometry, MRI or neutron activation).

During the discussion, Prof Shaldon directed me to the work of Jens Titze in Erlangen who is working on the effects of salt intake and salt storage in rats. Dr Titze's protocol for measurement of sodium includes stabilising the ionisation by measuring sodium in a 0.1% K solution, avoiding the use of plastic bottles, making his own standards, measuring in triplicate and checking the calibration after 10 samples. Dr Titze's main interest is the storage of

osmotically inactive sodium (and potassium) in the skin and connective tissue. He explained (by e-mail) that normal humans can store 2000 to 5000 mmol of sodium in an osmotically inactive state that does not cause thirst or lead to water retention. Accumulation and release of sodium from the inactive reservoirs is probably driven by changes in charge density. For example, negatively charged glycosaminoglycans (GAGs) in skin tissue could attract Na.

In a paper on sodium storage and hypertension in rats (20), Dr Titze's group speculated that sodium storage in an osmotically inactive compartment could be an alternative pathway for clearance of sodium from the extracellular space when sodium loads are excessive. The capacity to store sodium varied between different strains of rat. This could have implications in sodium profiling. However, Dr Titze pointed out that the role of osmotically inactive stores in dialysis would be difficult to study because humans cannot be subjected to studies that involve ashing tissues at up to 700°C and measuring sodium in the dissolved ashes! Sodium balance in HD, even when accurately measured, will not tell us where the sodium came from or how the distribution of osmotically active and inactive sodium changes.

Dr Kooman agreed with Prof Shaldon on the difficulty in obtaining precise sodium determinations and said that was why they chose to include conductivity measurements as a secondary analysis. However, he felt that the close correlation between the measured sodium removal and the ultrafiltration volume in HF suggested that the sodium measurements may have been reasonably reliable.

Prof Shaldon responded to this, emphasising the problem that conductivity is not a measure of sodium (see below). He also reminded the group that commercial acid is allowed an error of $\pm 2\%$ in its ionic content by the manufacturers, so that a nominal dialysate sodium of 140 mmol/l could be anywhere from 137 to 143 mmol/l. André Stragier confirmed that the tolerance for sodium in the Swedish standard, the European Pharmacopoeia and the AAMI standard is $\pm 2.5\%$. He also provided data from Gunnar Malmström in Sweden (where acid concentrate is routinely tested), which showed that, of 386 concentrates, 8% were outside the allowed limit.

Franta Lopot commented that the important point was that, whatever method you use, if you measure both the incoming and outgoing sodium concentration in the same way, you can get relevant figures. There may be a systematic shift of absolute value, but the results can be used for comparative studies. This approach was taken by Dr Kooman's group.

Measurement of conductivity balance

As mentioned above, the authors of the discussion paper looked at the conductivity balance as well as electrolyte balance. The conductivity balance was not well described or interpreted in the paper so the JC discussion provided some valuable clarification.

The conductivity balance, Hans Polaschegg explained, could be defined as the difference between the conductivity of the fresh and used dialysate, measured in mS/cm (at 25°C). Typically this balance would be less than 1 mS/cm. This balance is a measure of the blood-dialysate gradient and the dialyser clearance. On-line clearance monitors use sensors up and downstream of the dialyser to measure this balance at two different dialysate conductivities. These measurements are used to obtain the gradient, which is used to infer the plasma sodium, and the clearance. (Dr Polaschegg invented this method, which was patented by Fresenius in Germany in 1984 and the US in 1985). Every dialysis machine allowing on-line

clearance measurement can, in principle, measure the overall electrolyte balance by conductivity.

In the paper, the authors appear to have multiplied the difference in batch conductivity, presumably by sampling the fresh dialysate and the used dialysate collection, by the batch volume. There is some confusion as they have not used the correct units (which would be mS/cm.litre). The authors state that dialysate conductivity is mainly determined by sodium. This is correct for the absolute conductivity but not for the conductivity balance because relatively more potassium is removed and potassium ions contribute more to the conductivity than sodium ions, so potassium contributes around 25% to the total conductivity balance.

Dr Polaschegg said that the authors could have used the conductivity balance to cross-check the accuracy of the electrolyte measurements by calculating the expected conductivity balance from the electrolyte balances and comparing the result with the measured conductivity balance.

Jeroen Kooman thanked Hans Polaschegg for his insights and said he would be happy to provide the additional data required to make this cross-check. He explained that as both potassium and sodium balance were comparable between HF and HD, the equality of conductivity balance was still an argument for equality of sodium removal.

Later in the discussion Dr Polaschegg mentioned that an on-line technique using ion sensitive electrodes to allow the balance of individual electrolytes to be measured had been patented in the US in 1987 (21). He believes that this device, the 'Ionoflow' (22), still provides the most accurate measurement of sodium and potassium balance.

'Take-home messages'

The failure of this study to show a difference in haemodynamic stability between HD treatments with standard and low temperature dialysate may have been due to the small sample size, the exclusion of unstable patients, the use of saline dilution to measure PVR and the use of a study design, which did not account for the patients' pre-dialysis temperature. The authors and discussion contributors considered that there is good evidence, from basic physiology and clinical studies, that management of thermal energy transfer during dialysis can improve the haemodynamic stability. There are opportunities for well conducted studies to look at thermal control and the differences between patients.

From the lengthy discussion of sodium balance, it is clear that when measuring sodium levels for research projects, the method used must be carefully considered. This is especially important if you are measuring levels in both plasma and aqueous solutions (dialysate, urine). It is also very important to remember that the acid concentrate is allowed an error of up to 2% in sodium level, so the fresh dialysate sodium or infusate level must be measured when it is relevant to a study. Despite criticism of the methods used, the authors' conclusion that HF does not impair sodium removal was not challenged.

Conductivity balance could provide useful information for studies and on-line clearance monitors (with sensors before and after the dialyser) could provide accurate measurements of conductivity balance. Although absolute conductivity is primarily due to sodium, other ions (especially potassium) have a significant effect on the conductivity balance. On-line measurements using ion-selective electrodes can probably give the most accurate determination of electrolyte balance.

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(Please note that Hans Polaschegg says there is an error in equation 60)
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