Dialysate sodium levels for chronic haemodialysis (Protocol)

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[Intervention Protocol]

Dialysate sodium levels for chronic haemodialysis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review aims to look at the benefits and harms of using a low (< 138 mM) concentration of sodium in the dialysate of maintenance haemodialysis patients.

BACKGROUND

Description of the condition

Kidneys perform a vital role in controlling salt and water balance. People with end-stage kidney disease who are receiving maintenance haemodialysis rely on therapy to optimise salt and water levels. The current average concentration of salt (sodium) in dialysis fluid (dialysate) globally is 140 mM (Hecking 2011; Mc Causland 2012; Peixoto 2011), which is relatively high compared with concentrations used in the 1970s and 1980s. The use of higher sodium dialysate concentrations has been influenced by a desire to make dialysis more comfortable for patients, who often experience cramps and symptomatic drops in blood pressure (BP) (intradialytic hypotension) (Cybulsky 1985; Port 1973; Stewart 1972; Wilkinson 1977). Dialysate sodium concentrations that are higher than patients' blood sodium levels facilitate fluid removal during dialysis (ultrafiltration) and improve the likelihood of maintaining normal BP and heart function during dialysis. However, higher sodium levels mean that people on haemodialysis are often dialysing with a positive sodium gradient between their blood and the dialysate (Munoz Mendoza 2011; Peixoto 2011; Raimann 2009). By dialysis session end, patients often gain sodium, which increases thirst, fluid gain (interdialytic weight gain), and BP (hypertension). Consequently, most people on typical in-centre haemodialysis schedules, of four hours three times weekly, have chronic salt and water overload. Despite antihypertensive medications, hypertension is not controlled adequately (Agarwal 2003; Rahman 1999; Zazgornik 1997). Elevated BP and salt and water overload are recognised as key contributors to high levels of heart-related illness and cardiovascular deaths among people on dialysis (Charra 2004). Lower dialysate sodium concentrations may improve survival by ameliorating salt and water overload.

Sodium loading during haemodialysis is thought to account for a significant proportion of salt and water overload problems, and may occur in a number of ways: higher concentrations of sodium in dialysate, sodium profiling programs, saline used to treat intradialytic hypotension and to prime or wash-back the extracorporeal blood circuit.

Excessive body sodium content is thought to account for why people receiving maintenance haemodialysis have ongoing problems with excess thirst, fluid overload and high interdialytic weight gains (Davenport 2008; Fischbach 1988; Kimura 1984; Matsuoka 1990; Shepherd 1987; Stiller 2001; Van Stone 1982). In turn, these issues can lead to hypertension, left ventricular hypertrophy, congestive heart failure and ultimately, premature death (Charra 2004). Moreover, elevation in serum sodium concentration (above 135 mM) has been observed to directly increase BP by stiffening blood vessel walls (Oberleithner 2007).

Description of the intervention

Dialysate sodium concentration is considered to be low when a negative concentration gradient exists between the dialysate and the patient's bloodstream. Many studies do not measure patients' actual serum sodium or calculate the gradient. For this review, we will consider dialysate sodium levels below 138 mM to be low; 138 mM to 140 mM as neutral; and more than 140 mM as high.

How the intervention might work

Haemodialysis removes fluid and solutes through convection and diffusion. Convective losses of sodium during haemodialysis are dependent on ultrafiltration. Diffusive transfer of sodium depends on the direction of the sodium gradient between the dialysate and the patient's plasma. Plasma contains negatively charged proteins that may complex with sodium ions, reducing their availability to move across the dialyser membrane. Dialysate contains no proteins, therefore all ionised sodium is able to move across the membrane. This difference in available diffusible sodium is known as the Gibbs-Donan effect (Locatelli 1984). Dialysate sodium concentration is estimated from dialysate conductivity multiplied by 10 (Gotch 1990; Ragon 1985). Sodium gradient can be considered neutral if the dialysate sodium concentration is set around 2 mM below the plasma sodium concentration (Flanigan 2008; Lomonte 2011).

The sodium gradient becomes negative if dialysate sodium concentration levels are reduced below equivalence. Negative sodium gradient between the patient's blood and the dialysate induces diffusive sodium loss during that dialysis session. Desalination may lead to less thirst and lower interdialytic weight gains, which may lead to less extracellular fluid overload, reduced hypertension, and ultimately, reduced left ventricular hypertrophy and cardiovascular mortality.

However, when a negative sodium gradient exists osmotic drag for refilling the vascular space during ultrafiltration is reduced, which may cause haemodynamic instability and more episodes of intradialytic hypotension (Peixoto 2011; Santos 2008), especially when large ultrafiltration rates/volumes are required. Repeated intradialytic hypotension episodes are associated with temporary or permanent loss of heart contractility and congestive heart failure (Boon 2004; Bos 2000; McIntyre 2008; McIntyre 2014).

Why it is important to do this review

Recent observational data have signalled a possible association between lower dialysate sodium concentrations and higher mortality rates (Hecking 2012; Mc Causland 2012). Low dialysate sodium concentration may make dialysis uncomfortable, and patients dialysed with low sodium concentrations may experience sudden intradialytic hypotension, leading to temporary or permanent reductions in heart contractility (Boon 2004; Bos 2000; McIntyre 2008).

Whether chronic haemodialysis users are more at risk from complications of low or high sodium dialysate concentration may depend on their comorbidities. Clarification is needed about which competing risks are more important and relevant to achieving positive patient outcomes. This review will enable informed choices to be made about optimum dialysate sodium concentrations for both haemodialysis consumers and facilities providing haemodialysis.

OBJECTIVES

This review aims to look at the benefits and harms of using a low (< 138 mM) concentration of sodium in the dialysate of maintenance haemodialysis patients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) which evaluate the effects of using low dialysate sodium concentrations in maintenance haemodialysis patients. We will also include cross-over studies.

Types of participants

All patients undergoing maintenance haemodialysis for three or more months. No age, sex or comorbid inclusion or exclusion criteria will be applied.

Types of interventions

Comparisons between low (< 138 mM) and other dialysis sodium concentrations will be included.

1. Low (< 138 mM) dialysate sodium concentration versus high (> 140 mM) dialysate sodium concentration.
2. Low (< 138 mM) dialysate sodium concentration versus neutral (138 to 140 mM) dialysate sodium concentration.
3. Low (< 138 mM) average dialysate sodium concentration versus high (> 140 mM) average dialysate sodium concentration, for sodium profiled dialysis.
4. Low (< 138 mM) average dialysate sodium concentration versus neutral (138 to 140 mM) average dialysate sodium concentration, for sodium profiled dialysis.

We will exclude the following interventions.

1. Low dialysate sodium concentration interventions which are combined with other dialysis parameter interventions.
2. Interventions which are < 3 mM different from the comparison dialysate sodium.

Types of outcome measures

Intervention effects on the following outcome measures will be evaluated.

1. Interdialytic BP
2. Predialysis BP
3. Postdialysis BP
4. Intradialytic BP
5. Thirst
6. Episodes of intradialytic hypotension (as defined by study authors)
7. Episodes of cramp or discomfort during dialysis treatment session
8. Interdialytic weight gain
9. Left ventricular hypertrophy at the end of treatment
10. Predialysis serum sodium
11. Postdialysis serum sodium
12. Pulse wave velocity at the end of treatment
13. Left ventricular volume at the end of treatment
14. Extracellular fluid volume at the end of treatment
15. Mortality
16. Change in left ventricular ejection fraction at the end of treatment
17. Number of hospital admissions
18. Myocardial infarction
19. Stroke
20. Cardiovascular death

Primary outcomes Intradialytic hypotension (safety)Interdialytic weight gain (efficacy)

Primary outcomes

1. Intradialytic hypotension (safety)
2. Interdialytic weight gain (efficacy)

Secondary outcomes

1. Thirst
2. BP: predialysis, postdialysis, intradialytic and interdialytic time points
3. Frequency of episodes of cramp during dialysis treatment session
4. Predialysis serum sodium
5. Postdialysis serum sodium
6. Pulse wave velocity
7. Left ventricular volume
8. Extracellular fluid volume
9. Number of admissions to hospital
10. Mortality
11. Change in left ventricular ejection fraction
12. Left ventricular hypertrophy
13. Myocardial infarction
14. Stroke
15. Cardiovascular death.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Renal Group. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable, however studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
    - Participants and personnel
    - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes such as death, results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (BP, thirst scores, interdialytic weight gain, left ventricular hypertrophy), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

It is anticipated that most included studies will report change-from-baseline outcomes. A standard error of the mean (SEM) or CI will provide a measure of precision of the change from baseline. If neither SEM nor CI is reported, imputations will not be used. Studies that do not report change from baseline will be excluded from the meta-analyses.

It is not anticipated that we will find time to event data. However, if such data are identified we will refer to the *Cochrane Handbook for Interventions in Systematic Reviews* (Higgins 2011) for guidance.

Unit of analysis issues

We will include any cluster-RCTs that address altering dialysate sodium levels for haemodialysis. However, expert statistical advice will be sought to ensure that any included data have been analysed taking the cluster design into account before conducting meta-analyses.

Wherever possible data from the end of the first phase of cross-over studies will be included in the meta-analysis; the preferred approach will be approximation of a paired analysis.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing or writing to corresponding authors) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and haemodialysis withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity will be analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could relate to their age, time on dialysis, era in which they were receiving dialysis, residual kidney function, whether they were on conventional or extended hours dialysis regimes, predialysis serum sodium and if diabetes or ischaemic heart disease comorbidities existed. Heterogeneity in interventions may be related to duration of intervention, magnitude of difference between sodium concentrations, and whether sodium concentrations were individualised or changed on a group level. Heterogeneity in study design may be related to the sample size, whether participants were randomised or crossed over, and how BP outcomes were measured. Adverse effects will be tabulated and assessed using descriptive techniques because these are likely to differ according to interventions used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared with no treatment or another agent.
Heterogeneity will be investigated by analysing subgroups according to the following parameters.

Population characteristics

- Presence or absence of residual kidney function (defined as urine output greater than or less than 500 mL/24 hours)
- Age (< 18 years and ≥ 18 years)
- Conventional or extended hours dialysis
- Presence or absence of comorbidities (diabetes or ischaemic heart disease)
- Predialysis serum sodium (< 135 mM or ≥ 135 mM)
- Era (pre or post 2000)
- Time on dialysis (< 12 months or ≥ 12 months).

Intervention characteristics

- Duration of intervention (< 4 weeks or ≥ 4 weeks)
- Individualised or group change in dialysate sodium
- Magnitude of difference between dialysate sodium (3 mM or > 3 mM)
- Dialysate buffer (acetate or bicarbonate).

Study design characteristics

- Sample size
- Randomised
- Cross-over
- BP measurement (predialysis, intradialytic, postdialysis or interdialytic).

Sensitivity analysis

We will perform sensitivity analyses to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country
- Repeating the analysis excluding any cross-over studies with a washout period of less than one week.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. dialysis:ti,ab,kw 2. (hemodialysis or haemodialysis):ti,ab,kw 3. (hemodiafiltration or haemodiafiltration):ti,ab,kw 4. (hemofiltration or haemofiltration):ti,ab,kw 5. ultrafiltration:ti,ab,kw 6. {or #1-#5} 7. (dialysis next solution*):ti,ab,kw 8. (dialysis next fluid*):ti,ab,kw 9. dialysate*:ti,ab,kw 10. {or #7-#9} 11. sodium:ti,ab,kw 12. {and #6, #11} 13. {and #10-#11} 14. {or #12-#13}
MEDLINE	1. Renal Dialysis/ 2. exp Ultrafiltration/ 3. dialysis.tw. 4. (hemodialysis or haemodialysis).tw. 5. (hemodiafiltration or haemodiafiltration).tw. 6. (hemofiltration or haemofiltration).tw. 7. ultrafiltration.tw. 8. or/1-7 9. exp dialysis solutions/ 10. dialysate*.tw. 11. dialysis solution*.tw. 12. dialysis fluid*.tw. 13. or/9-12 14. Sodium/ 15. (sodium adj5 (concentration* or level or levels or load or loading)).tw. 16. (sodium adj5 (low* or reduc* or decreas* or high* or increas* or alter*)).tw. 17. (sodium adj5 (profil* or ramp* or model*)).tw. 18. or/14-17 19. and/13,18 20. and/8,18 21. or/19-20
EMBASE	1. Hemodialysis/ 2. Hemofiltration/ 3. Hemodiafiltration/ 4. Dialysis/ 5. Ultrafiltration/ 6. (hemodialysis or haemodialysis).tw.

(*Continued*)

	7. (hemofiltration or haemofiltration).tw. 8. (hemodiafiltration or haemodiafiltration).tw. 9. dialysis.tw. 10. ultrafiltration.tw. 11. or/1-10 12. Hemodialysis Fluid/ 13. Dialysate/ 14. dialysate*.tw. 15. dialysis solution*.tw. 16. dialysis fluid*.tw. 17. or/12-16 18. Sodium/ 19. Sodium Balance/ 20. Sodium Load/ 21. (sodium adj5 (concentration* or level or levels or load or loading)).tw. 22. (sodium adj5 (low* or reduc* or decreas* or high* or increas* or alter*)).tw. 23. (sodium adj5 (profil* or ramp* or model*)).tw. 24. or/18-23 25. and/17,24 26. and/11,24 27. or/25-26

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of

(*Continued*)

	identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plau-

(*Continued*)

	sible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem

(*Continued*)

	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: JD, MM
2. Study selection: JD, MM
3. Extract data from studies: JD, MM, AV
4. Enter data into RevMan: JD
5. Carry out the analysis: JD, MM, AV
6. Interpret the analysis: JD, MM, AV
7. Draft the final review: JD
8. Disagreement resolution: AV
9. Update the review: JD

DECLARATIONS OF INTEREST

None known.