PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Magnesium in chronic hemodialysis (MAGIC-HD): a study protocol for a randomized controlled trial to determine feasibility and safety of using increased dialysate magnesium concentrations to increase plasma magnesium concentrations in people treated with hemodialysis.
AUTHORS	Leenders, Nicoline; Douma, Caroline; Hoenderop, Joost; Vervloet, Marc

VERSION 1 – REVIEW

REVIEWER	Canaud, Bernard Montpellier University School of Medicine, Nephrology
REVIEW RETURNED	22-May-2022

GENERAL COMMENTS	Leenders NHJ and coworkers are submitting the medical rationale and the study design aiming to increase plasma magnesium concentrations by increasing dialysate magnesium concentration approach in a stepwise approach (from 0.5, 0.75 to 1.0mM/l) in hemodialysis patients. This short term RCT study (8 weeks) explored mainly safety of such an approach, targeting a maximum plasma magnesium of 1.25 without ECG abnormalities. In addition, Holter ECG and pulse wave velocity will be recorded at various time points to secure the approach. Rationale is perfectly founded. Study design and analysis plan are well described. There is no real concern from a safety perspective. My main concerns are the following: 1. Dialysis modality is not described in term of treatment time, frequency, dialysis modality (HD versus HDF), operating conditions (blood flow, dialysate flow, dialyzer surface area….) and in addition there is no indication of clinical performances targeted (Kt/V for example). 2. Acidifier of bicarbonate dialysate is not mentioned (acetic acid, citric acid or another weak acid…) this is crucial for assessing magnesium and calcium concentrations. 3. Ionized plasma magnesium concentration is not considered in this analysis plan. That should be considered since ionized magnesium is the active compound strongly affected by albumin concentration and pH. Therefore, it would be interesting to know how the investigators are planning to consider this important factor. 4. Unfortunately, magnesium mass balance is not part of the study plan, meaning that something will be missing at the end of the study to interpret plasma magnesium changes. 5. Last, but not least, dialysate calcium concentration is not mentioned. This is a crucial point in the study when considering

	magnesium effects on cardiac functionality or cardiac rhythm as well as on PWV. That should be given as additional information. 6. Magnesium-based phosphate binders should be excluded from the study. Also, proton pump inhibitors should be kept constant in case of patients are using them. 7. PTH levels should be also monitored along the 8 weeks study

REVIEWER	Pirklbauer, Markus Medical University Innsbruck, Internal Medicine IV
REVIEW RETURNED	01-Jun-2022

GENERAL COMMENTS	The present study protocol describes an ongoing feasibility & safety study (MAGIC-HD) evaluating the effect of stepwise increase of dialysate magnesium concentation on pre-dialysis serum magnesium concentrations over a 8 week periode in chronic HD patients. The study is about to finish patient recruitment, and thus, first results can be expected rather soon after publication of the study protocol. These results are of substantial relevance for planning future outcome studies with respect to individualized dialysate magnesium concentrations. The trial design is appropriate for the research question raised and the results are of potentially high relevance for the HD population. Thus, I recommend publication of the protocol of this ethics committee approved ongoing randomized controlled trial.

VERSION 1 – AUTHOR RESPONSE

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We hereby provide our point by point reply to the questions raised by the reviewers.

Reviewer 1
Leenders NHJ and coworkers are submitting the medical rationale and the study design aiming to increase plasma magnesium concentrations by increasing dialysate magnesium concentration approach in a stepwise approach (from 0.5, 0.75 to 1.0mM/l) in hemodialysis patients. This short term RCT study (8 weeks) explored mainly safety of such an approach, targeting a maximum plasma magnesium of 1.25 without ECG abnormalities. In addition, Holter ECG and pulse wave velocity will be recorded at various time points to secure the approach.
Rationale is perfectly founded. Study design and analysis plan are well described. There is no real concern from a safety perspective.

We are grateful for these encouraging words, and the acknowledgement that the rationale is well founded, methods are well described and that there are no safety concerns.

My main concerns are the following:
1. Dialysis modality is not described in term of treatment time, frequency, dialysis modality (HD versus HDF), operating conditions (blood flow, dialysate flow, dialyzer surface area….) and in addition there is no indication of clinical performances targeted (Kt/V for example).

Dialysis frequency is 3 times weekly, as is described in the methods section, under subheading "Study procedures and participant time line" in the following sentence: "During the trial, all participants receive three times weekly hemodialysis sessions according to their regular schedule."

The other variables mentioned by the reviewer are recorded in the study and were summarized in short by the sentence “Furthermore, persons’ characteristics are recorded at baseline and characteristics of the dialysis are recorded weekly for the time of dialysis after the long interdialytic interval and for every dialysis during the first and fifth week of intervention.”
We now specified this further for clarity and added the variables as follows: “Furthermore, persons’ characteristics are recorded at baseline and characteristics of the dialysis are recorded at baseline and weekly for the time of dialysis after the long interdialytic interval and for every dialysis during the first and fifth week of intervention. Recorded dialysis characteristics include modality (hemodialysis or hemodiafiltration), vascular access (catheter, fistula or graft), estimation of dialysis efficiency (Kt/Vurea per session according to Daugirdas' formula), treatment time per session, blood flow, dialysate flow and ultrafiltration volume”

2. Acidifier of bicarbonate dialysate is not mentioned (acetic acid, citric acid or another weak acid…) this is crucial for assessing magnesium and calcium concentrations.

The dialysate concentrates that are used in the study are mentioned in the methods section, under subheading “intervention” as follows: “For the respective magnesium concentrations, six dialysis concentrates are used in weeks 1-9 (Hemodialysis A-concentrate, D761, D987, D907, D283, D961 and D908, MTN Neubrandenburg GmbH, Neubrandenburg, Germany).”
The mentioned dialysates are commercially available products with established contents. Acidifier in these dialysates is acetate. We did not include citrate dialysis in the study. These dialysates have a fixed sodium and calcium concentration, respectively 138 mmol/L and 1.25 mmol/L. For clarity, we now added this in the manuscript as follows: “For the respective magnesium concentrations, six dialysis concentrates are used in weeks 1-9 (Hemodialysis A-concentrate, D761, D987, D907, D283, D961 and D908, MTN Neubrandenburg GmbH, Neubrandenburg, Germany). In the mineral composition of these concentrates, besides potassium based on individual needs, only the amount of magnesium chloride is different. Calcium concentration in these dialysates is 1.25 mmol/L and the acidifier is acetatic acid.”

3. Ionized plasma magnesium concentration is not considered in this analysis plan. That should be considered since ionized magnesium is the active compound strongly affected by albumin concentration and pH. Therefore, it would be interesting to know how the investigators are planning to consider this important factor.

Indeed, in this study total magnesium concentration is measured, not ionized magnesium, while especially the ionized (free) magnesium is amenable for dialytic clearance. However, total plasma magnesium has been extensively used in clinical studies and has shown to be associated with many clinically relevant outcomes in observational studies, as mentioned in the introduction of the manuscript. Therefore, total plasma magnesium has proven a relevant variable in the hemodialysis population. Moreover, ionized magnesium measurement is not generally available in routine medical care and therefore, this measurement is not easily implementable. On the contrary, total plasma magnesium measurement methods are generally available in routine medical care and therefore measurement of this parameter can be easily implemented in routine patient care.

4. Unfortunately, magnesium mass balance is not part of the study plan, meaning that something will be missing at the end of the study to interpret plasma magnesium changes.

We thank the reviewer for this suggestion and agree that magnesium mass balance would have been an interesting additional parameter. However, collection of dialysis effluent is not included in this study protocol and therefore, unfortunately, we are not able to calculate magnesium mass balance. However, although we do not measure mass balance, we do think that plasma magnesium is a relevant outcome parameter, because previous observational studies have demonstrated the

relevance of this concentration by showing an inverse association between plasma magnesium concentration and several clinical outcomes, as is described in the introduction of the manuscript.

5. Last, but not least, dialysate calcium concentration is not mentioned. This is a crucial point in the study when considering magnesium effects on cardiac functionality or cardiac rhythm as well as on PWV. That should be given as additional information.

We thank the reviewer for this suggestion and agree that this is relevant information. We now added this information in the manuscript (see also the answer above to comment 2)

6. Magnesium-based phosphate binders should be excluded from the study. Also, proton pump inhibitors should be kept constant in case of patients are using them.

Indeed, a change of proton pump inhibitors or magnesium-based phosphate binders could influence the results. Therefore, these are kept constant during the study, as is mentioned in the manuscript at the end of paragraph “study procedures and participants time line” as follows: “changes in prescription of proton pump inhibitors and magnesium-containing supplements, laxatives and phosphate binders will be avoided if clinically allowed.” After inclusion, the treating physician is requested by the researchers not to make changes in prescription of these medications. This can be verified and taken into account by the researchers because prescribed medication is recorded at baseline and at the end of the study (week 8). We chose not to exclude patients that use magnesium-based phosphate binders, because we aimed to include participants representative for the prevalent dialysis population. To take into account possible effects of magnesium-based phosphate binders, changes in this medication are avoided during the study, and medication use is recorded and can be taken into account in the analysis.

7. PTH levels should be also monitored along the 8 weeks study

We agree that PTH levels are relevant and should be recorded along the study. We therefore measure PTH levels at baseline, half-way and at the end of the study. This is mentioned in the paragraph “patient interventions and participants time line” in the methods section as follows: “In addition, in week 1, 5 and 9, blood is collected for measurements of potassium, bicarbonate, calcium, albumin, phosphate, parathyroid hormone (PTH), hemoglobin and C-reactive protein (CRP).”

Reviewer 2

The present study protocol describes an ongoing feasibility & safety study (MAGIC-HD) evaluating the effect of stepwise increase of dialysate magnesium concentation on pre-dialysis serum magnesium concentrations over a 8 week periode in chronic HD patients. The study is about to finish patient recruitment, and thus, first results can be expected rather soon after publication of the study protocol. These results are of substantial relevance for planning future outcome studies with respect to individualized dialysate magnesium concentrations. The trial design is appropriate for the research question raised and the results are of potentially high relevance for the HD population. Thus, I recommend publication of the protocol of this ethics committee approved ongoing randomized controlled trial.

We are delighted that the reviewer underscores the relevance of the study, concludes that the design is appropriate and recommends publication of the protocol.