Author's response to reviews

Title: The Efficacy and Safety of Lanthanum Carbonate on Chronic Kidney Disease Mineral and Bone Disorder in Dialysis Patients: A Systematic Review

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Author's response to reviews: see over
Dear Bjorn Meijers:

Thank you so much for the careful review and very good suggestion to our systematic review. The response to your questions was list below.

1. **Major compulsory revisions**

   Consider including the following manuscripts for systematic review. If the authors decide not to include these, please argue why not to include it.

   - Xu et al. BMC Nephrology 2013
   - Kasai Ther Apher Dial 2012

   **Author’s response:** When we did the systematic review, the latest date for the article search was Dec.31, 2012. That’s why the manuscript of Xu 2013 was not included at that time. We agree with you and consider this manuscript is also very important. In the amended version of our systematic review, we include this article and changed the latest date for the search to March 31, 2013. Literature search was performing again and no other new manuscript was founded.

   Kasai Ther Apher Dial 2012 is a randomized cross-over study comparing sevelamer (SH) and lanthanum (LC). We agree with your opinion that the comparison between sevelamer and lanthanum is very important because both of them are the new non-aluminum, non-calcium phosphate binders. When we did the literature search, we did found two randomized crossover studies comparing SH and lanthanum (Satoshi Kasai 2012 and Sprague S.M 2009). The authors combined the data of phase 1 and phase 2 (before and after the exchange of treatments) together to do the comparison. To avoid insufficient wash-out, we intended to use the data of first phase (before exchange) which was not available. Because there was no reply from the authors after we sent e-mails to inquiring the data, we abandoned these two trials. However, we do consider the comparison between SH and LC is of great importance as you advised. We consulted the statistic professor of the Chinese Evidence-based Medicine Center in our university and were informed such comparison could be adopted if the data of first phase was not available. We then added these two manuscripts in our meta-analysis.

   After the inclusion of these three manuscripts, we did the meta-analysis again and changed the results correspondingly.

2. **Minor Essential Revisions**

   Significant review of English grammar and spelling is warranted. Please find a non-exhaustive list below:

   **2.1 Title:**
   “patients with dialysis”, please change into “dialysis patients or patients on dialysis”.

   **Author’s response:** We have changed our title as “dialysis patients or patients on dialysis”.

   **2.2 Abstract**
   - Background: first sentence is redundant

   **Author’s response:** We have deleted this sentence.

   - Methods: Avoid abbreviation without first mentioning the full descriptive term
RCT: randomized controlled trial

**Author’s response:** Thank you for your remind. We have checked the whole article and added the full descriptive term when the abbreviation first mentioned.

- Results:
  *“with 3142 pt”, please change into “with a total of 3142 pt”.

**Author’s response:** It has been change into “with a total of 3789 patients” (new manuscripts included and more patients included correspondingly).

*Statistical instead of statistics

**Author’s response:** It has been change into “statistical”.

*Limited number of trials instead of limited trials

**Author’s response:** It has been change into “limited number of trials”.

*Superiority instead of priority

**Author’s response:** It has been change into “superiority”.

*Appeared to have a higher instead of appeared a higher

**Author’s response:** It has been change into “appeared to have a higher”.

- Conclusions: *good instead of well efficacy (see also 2nd paragraph background main body)

**Author’s response:** It has been change into “good” both in abstract and 2nd paragraph background main body.

*Except for instead of except.

**Author’s response:** It has been change into “except for”.

2.3 Background

- First paragraph:
  *suffered instead of were suffered

**Author’s response:** It has been change into “suffered”.

*Increasing evidence showed “that”…

**Author’s response:** It has been change into “Increasing evidence showed that”.

-Second paragraph last sentence: making it instead of makes it

**Author’s response:** It has been change into “making it”.

-Third paragraph last sentence: leave in (changing bone morphology)

**Author’s response:** It has been change into “changing bone morphology”.

-Last paragraph: mainly focusing instead of focused

**Author’s response:** It has been change into “focusing”.

2.4. Methods

- General remark: use uniform verb tenses (e.g., search strategy: …who discarded studies that are not applicable…will be retained).

**Author’s response:** Yes, we have checked the verb tenses, and used the past tense in this paragraph.

- Interventions: routine treatment: was use of calcimimetics allowed, did all studies include dietary phosphate restriction in the routine treatment?

**Author’s response:** Yes, use of calcimimetics was allowed in all the studies when needed and has been identified it in the part of Interventions. Only the study indicated the use of calcimimetics was parallel was included. We amended as “Other medications treating CKD-MBD, such as calcitriol and calcimimetics, can be used
when needed, but the use of such medications should be parallel between treatment group and control group”. And in the result part, we added “Four studies[17, 20, 21, 29] used calcitriol and one study[17] used calcimimetics in routine treatment and the baseline of the usage of above medication were parallel between the intervention group and control group in all these studies.”

Dietary phosphate restriction was only mentioned in 2 studies (S.-S Chiang 2005 and Jing Xu 2013). One study (Takashi Shigematsu 2008) indicated “the contents of the patients’ daily diet and dialysis conditions remained unchanged throughout the study period”. Another study (A. J. Hutchison) just performed dietary assessments. Other studies did not mention dietary restriction. Therefore, we added “Dietary phosphate restriction was not mandatorily required” in the amended version.

- Primary outcome: CV events: please specify
  Author’s response: CV events mean fatal or nonfatal myocardial infarction, fatal or nonfatal cerebrovascular event (stroke), or the development of coronary artery disease. And we identified it in the part of primary outcome.

- Secondary outcomes: please specify “control rate of serum P” (percentage of patients with P below ULN?, …?)
  Author’s response: It is an important issue to specify the controlled phosphate level. However, the target of controlled serum phosphorous level varied from 5.5mg/dl (1.78mmol/L) to 5.9mg/dl (1.9mmol/L) in different studies. The inconformity in phosphate controlled level will result in bias for the outcome evaluation and meta-analysis. Therefore, we decided to cancel the outcome measurement of “control rate of serum P”.

2.5 Results:
*search result: inconformity, change into for example none of them met…
  Author’s response: It has been changed into “…were excluded because of none of them met inclusion criteria”

*please leave “Error! Bookmark not defined”
  Author’s response: It has been deleted.

*study quality: random instead of randomly
  Author’s response: It has been changed into “random”.

*effect on all-cause mortality: patients using instead of use no significant instead of not a
  Author’s response: It has been changed into “Two studies [19, 23] reported all-cause mortality between patients using LC and other phosphate binders. There was no significant difference in …”.

*effect on CV events: experienced at least one instead of appeared once
  Author’s response: It has been changed into “experienced at least one”.

*effect on vessel calcification: no trials instead of trails
  Author’s response: It has been changed into “no trials”.

*bone disorder: compared in 8 other instead of other 8
  Author’s response: It has been changed into “The serum phosphorus level was compared in ten other studies…” (more studies included).

*people who were treated instead of treated
**Author’s response:** It has been changed into “People who were treated with …”.

*ROD: Avoid abbreviation without first mentioning full term (renal osteodystrophy)

**Author’s response:** We had added the full term as “renal osteodystrophy (ROD)”.

### 2.6. Discussion:

*the description of the association between lanthanum and lower rate of intradialytic hypotension is too extensive and hypothetical.

**Author’s response:** The mechanism of intradialytic hypotension is very complicated. There’s only one trial (W.F. Finn 2006) showed LC had lower risk of intradialytic hypotension compared with NCBs and we agree the discussion to this part is too hypothetical. More trials are needed to test the beneficial effect of LC on lowering the risk of intradialytic hypotension and we get rid of the description of this part

*last sentence: evaluating instead of evaluates

**Author’s response:** It has been changed into “Therefore, a systematic review evaluating the health economic effectiveness…”.

*p17: while Spasovski, please change into, In contrast, Spasovski…

**Author’s response:** It has been changed into “In contrast, Spasovski…” (p18)

*p18: to better detect instead of detecting

**Author’s response:** It has been changed into “To better detect the effect of LC on ROD…”.

*p18: as the evaluation of diarrhea…it may vary with individual. This sentence is redundant, please leave it.

**Author’s response:** It has been deleted.

### 2.7 Table 1: The outline must be more uniform (e.g., use brackets for all descriptions or for none of them)

**Author’s response:** Yes, the table has been united the formatted.

Table- Placebo # placebo

**Author’s response:** Yes, we have corrected the spelling mistake in the table.

**Quality of written English:** Not suitable for publication unless extensively edited.

**Author’s response:** We have extensively edited the whole article, including correcting spelling and grammar mistakes, writing more fluently to meet the standard for publication.

Answers to Francesco Locatelli

**Reviewer's report:**
The manuscript 'The Efficacy and Safety of Lanthanum Carbonate on Chronic Kidney Disease Mineral and Bone Disorder in Patients with Dialysis A Systematic Review' by Chenglong Zhang, Ji Wen, Zi Li and Junming Fan is unbalanced being too much Lantanum oriented. The sevelamer is not a new phosphate binder (as is not LC) moreover the risk of accumulation (liver, bones etc) should be discussed in detail
quoting and discussing the related paper being the major concern in using the drug in everyday clinical practice. The lack of other so call "pleiotropic effects" in comparison with sevelamer should also be discussed.

Author’s response: Thanks so much for the very important suggestion. We did find two cross-over studies comparing SH and LC when we did the literature searching. The authors combined the data of phase 1 and phase 2 (before and after the exchange of treatments) to do the comparison and the data of first phase was not available. Because there was no reply from the authors after we sent e-mails to inquiring the data, we abandoned these two trials. However, we do consider the comparison between SH and LC is of great importance as you and the other reviewer advised. We consulted the statistic professor of the Chinese Evidence-based Medicine Center in our university and were informed such comparison could be adopted if the data of first phase was not available.

We then added these two manuscripts in our meta-analysis and found SH and LC were similarly effective at controlling serum calcium and phosphate levels. Previous studies had shown that SH had “pleiotropic effects” as lowering cholesterol and anti-inflammatory effect by lowering C-reactive protein and fetuin A and ameliorating hyperuricemia. Our meta-analysis demonstrated SH has lower serum level of total cholesterol and LDL cholesterol but the included studies did not compare inflammatory parameters such as CRP and fetuin A. The included studies did not compare the serum bicarbonate and potassium level and the risk of metabolic acidosis and hyperkalemia was unknown. We recommended future study is needed to compare such parameters and the comparison between LC and sevelamer carbonate is recommended. Overall, our systematic review showed that SH and LC were comparable treatments for controlling serum phosphate and calcium levels, and that both compounds were safe. We had added the comparison between LC and SH in the manuscript and changed the results and discussion accordingly.