Peer Review File

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RESPONSES TO REVIEWER A'S COMMENTS:

Comment 1: This study retrospectively examines the actual state of hypermagnesemia and its risk factors in end-stage cancer patients. The findings warn against the vague use of magnesium oxide in patients with poor renal function. The paper is considered suitable for publication in the Annals of Palliative Medicine.

Reply 1: Thank you for your appreciation of our manuscript. We corrected the manuscript in accordance with your comments.

Comment 2: Poor prognosis was a risk factor for hypermagnesemia. Is Hypermagnesemia Possibly Poor in Prognosis?

Reply 2: As you pointed out, the results of this study show that poor prognosis is a risk factor for hypermagnesemia. On the other hand, as mentioned in the introduction of this manuscript, Alsirafy et al. reports that hypermagnesemia is a risk factor for poor prognosis. In order to express this more clearly, we revised the Introduction.

Changes in the text 2: We have changed following text (page 4 line 11 to line 13) from:

"Another study has shown that hypermagnesemia is even more prevalent in palliative care cases—occurring in 13% of patients—and is correlated with early hospital death (5)."

to

“Another study has shown that hypermagnesemia is even more prevalent in palliative care cases—occurring in 13% of patients—and is correlated with **poor prognosis in end-stage cancer patients** (6).”

Comment 3: Sensitivity analysis detected constipation as a significantly lower predictor of hypermagnesemia, assuming hypermagnesemia in all cases where serum magnesium levels were not measured (Table 4). With constipation, the risk of hypermagnesemia decreases (OR=0.47). With constipation, it is estimated that the frequency and amount of magnesium oxide used will increase. The results seem to be the opposite.

Reply 3: Sensitivity analysis of this study detected poor prognosis, renal dysfunction, and magnesium oxide laxative use as risk factors of hypermagnesemia, assuming no hypermagnesemia in all cases where serum magnesium levels were not measured (Table 3). This result was consistent with the main result. The incidence of hypermagnesemia was 23.08% in cases where serum magnesium levels were measured. We considered that assuming hypermagnesemia in all cases where serum magnesium levels were not measured was a more extreme setting than assuming no hypermagnesemia. Sensitivity analysis of this study detected constipation as a significantly lower predictor of hypermagnesemia, assuming hypermagnesemia in all cases where serum magnesium levels were not measured. As you pointed out, this result is in direct contradiction to previous reports that constipation is a risk factor for hypermagnesemia. This means that assuming hypermagnesemia in all cases where serum magnesium levels were not measured is considered too extreme because the results were the opposite of what has been previously reported. Even in such an extreme setting, poor prognosis, renal dysfunction, and magnesium oxide laxative use did not change. This result indicated that these three risk factors are robust.

Changes in the text 3: We have changed following text (page 12, line 11 to page 13, line 6) from:

“The sensitivity analysis of magnesium deficiency in extreme settings showed little change, suggesting that this result was fairly robust.

to

“The result of sensitivity analysis, assuming no hypermagnesemia in all cases where serum magnesium levels were not measured, is consistent with the main result (Table 3). On the other hand, the result of the sensitivity analysis, assuming hypermagnesemia in all cases where serum magnesium levels were not measured, was not consistent with the main result, and shows that constipation is a significantly lower predictor of hypermagnesemia (Table 4). This result contradicts previous reports that constipation is a risk factor for hypermagnesemia (7-12). Because the incidence of hypermagnesemia was 23.08% in cases where serum magnesium levels were measured, we determined that assuming hypermagnesemia in all cases where serum magnesium levels were not measured was a more extreme setting compared with assuming no hypermagnesemia in all cases where serum magnesium levels were not measured. Even in a more extreme setting, the result of sensitivity analysis was consistent with the main result with the exception of constipation. This suggests that this result was fairly robust.”

Comment 4: Was the difference in dosage and usage of magnesium (scheduled medication or independence) taken into consideration?

Reply 4: All participants in this study received a magnesium oxide laxative as a scheduled medication. Some patients, at the discretion of the nurse or the patient, were given some or all of the prescribed magnesium oxide, but may not have taken it, which I was unable to assess.

Different cut-off values of oral magnesium oxide laxative doses for the development of hypermagnesemia have been previously reported. Therefore, we calculated cut-off values using receiver operating characteristics (ROC) curve method in the preliminary survey, which was performed in September and October 2019. The cut-off value (area under the ROC curve: AUC) of the oral magnesium oxide laxative dose was 330 mg/day (0.67). Because the minimum dose of oral magnesium oxide laxative in our hospital is 330 mg/day, we did not set a cut-off value in this study, and the presence or absence of oral magnesium oxide laxative was considered.

Changes in the text 4: We have added following text (page 6 line 5 to line 12):

"Because different cut-off values of oral magnesium oxide laxative doses for the development of hypermagnesemia have been previously reported (11, 12), we performed a preliminary survey in September and October 2019, and the cut-off value was calculated by the receiver operating characteristics (ROC) curve method. The cut-off value (area under the ROC curve: AUC) of oral magnesium oxide laxative dose was 330 mg/day (0.67). Because the minimum dose of oral magnesium oxide laxative in our hospital is 330 mg/day, we did not set a cut-off value in this study, and the presence or absence of oral magnesium oxide laxative was considered."

Comment 5: Hypermagnesemia is evaluated only by the upper limit of serum magnesium test. Is there any actual manifestation of hypermagnesemia?

Reply 5: Many of the patients whose serum magnesium was above the upper limit had neuromuscular problems such as weakness, cardiovascular problems such as arrhythmias and hypotension, and gastrointestinal problems such as nausea and vomiting. However, we were unable to determine whether it was manifested as a symptom of end-of-life cancer or hypermagnesemia.

RESPONSES TO REVIEWER B'S COMMENTS:

Comment 1: Thank you for submitting the manuscript. I have read your paper very carefully. The topic covered presents some original ideas and I appreciated your work. The manuscript is clear, legible and honestly addresses the limits.

Reply 1: Thank you for your appreciation of our manuscript. We revised the manuscript according to your comments.

Comment 2: I suggest two minor revisions. In the introduction I would like you to

explain the physiological role of magnesium, so as to better understand how hypermagnesemia can represent an important risk for fragile patients. For this reason, I suggest this reference: “Hypermagnesemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Jan 20. PMID: 31747218 NBK549811”.

Reply 2: We revised the manuscript according to your comments.
Changes in the text 2: We have added following text (page 4 line 2 to line 5):

“Normally, an adult individual possesses about 25 g of magnesium, which is necessary for life-sustaining functions such as enzymatic action, transporters, and the synthesis of nucleic acids. Abnormalities in magnesium also affect other electrolytes such as sodium, calcium and potassium, so early detection and treatment is recommended (1).”

Furthermore, I have added the following reference and have revised the reference numbers.

1. Cascella M, Vaqar S. Hypermagnesemia. StatPearls, 2020. https://www.ncbi.nlm.nih.gov/books/NBK549811/#article-23189.s1 [Cited 2020 July 9].

Comment 3: In this way it will be more evident that hypermagnesemia is a health risk. You wrote within the limits of this paper that the study was conducted in one center. In my opinion, it would be more appropriate in the conclusions to specify that other multicenter studies are needed to better validate the results obtained in this study.

Reply 3: We revised the manuscript according to your comments.

Changes in the text 3: We have added following text (page 15 line 10 to line 11):

“Other multicenter studies are needed to validate the results of this study.”

Comment 4: In conclusion, the paper is well written and very interesting. I hope these

comments are useful.

Reply 4: Thank you very much for your comments. We are deeply grateful for the time and energy you spent reviewing our manuscript.