PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for thiamine and folic acid in the treatment of cognitive impairment in maintenance hemodialysis patients: A prospective, randomized, placebo-controlled, double-blind, multi-center study
AUTHORS	Lu, Renhua; Gu, Le-yi; Zhang, Weiming; Guo, Yongping; Zang, Xiujuan; Zhou, Yan; Yu, Ling; Pan, Shuting; Pang, Huihua; Liu, Shang; Xie, Kewei; Li, Ping; Zeng, Xiaojun; Lu, Yifei

VERSION 1 – REVIEW

REVIEWER	Erken, Ertugrul Kahramanmaras Sutcu Imam Universitesi, Nephrology
REVIEW RETURNED	02-May-2021

GENERAL COMMENTS	This study aims to evaluate the effects of combined thiamine and folic acid treatment on cognitive functions in chronic hemodialysis patients. This is the study protocol of a prospective, randomized, placebo-controlled trial. The research question is clearly outlined. The researchers have also done a pilot study to determine their study goals and the sample size. This manuscript is the detailed methodology of a multi-ceter study. Therfore, the results of the current study are not included. According to the literature it may be wise to make a 1 point decrease in the MoCA cutoff values in this specific study population. This study (when finished) may lead to very interesting, scientific and valuable results.

REVIEWER	Chen, Yi-Lung Chang Gung Memorial Hospital
REVIEW RETURNED	20-May-2021

GENERAL COMMENTS	This manuscript conducted a randomized, placebo-controlled, double-blind study to examine Thiamine and folic acid in the treatment of cognitive impairment in maintenance hemodialysis. This is an important issue and the most study design in this study is adequate. I have some suggestions to authors for improving their study design and presentation. The full name of Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) should be spelled out when it first occurred in this manuscript. Some grammar tense is not consistent in this manuscript. For example, " Even if the subject is unable to return to the study center for visits, the investigator will complete all available data on the Case Report Form (CRF) and record the reason.." and " It will be listed separately that the number of subjects selected…"

	But in their discussion, "The subjects were randomly divided into treatment group… The authors should consider the English editing for their manuscript." The DPI of their Figure 1 is too low, please provide a better solation of a new Figure, with DPI at least 300, or 600 which is even better. For the statistics, some more corrected analytical strategies can be used in this study. First, the authors mentioned within comparison and between comparison using repeated measure ANOVA, and simple oneway ANOVA. However, I think the generalized estimating equations (GEE) can be more powerful to analyze their data. Second, authors mentioned that Kaplan-Meier survival curve was used for survival analysis. However, the endpoints the authors used were ADAS-Cog score, serum thiamine, folate, and homocysteine level, cranial functional magnetic resonance imaging, and prognosis. I cannot see any binary variable for survival analysis. Please specify the outcomes they want to use for survival analysis.

REVIEWER	Hwang, Seun Deuk Inha University Hospital
REVIEW RETURNED	20-May-2021

GENERAL COMMENTS	1. This study enrolled patients with MoCA scores below the standard. However, is it not good to use the ADAS-Cog score, which is the primary endpoint, instead of using the MoCA score when enrolling patients with the ADAS-Cog score for the primary endpoint? Of course, the MoCA score is also finally obtained, but is it good to predict and evaluate the patient's cognitive impairment prediction and response when the enrolled index and the primary endpoint index are different? 2. Is the amount of thiamine and folic acid mentioned in the study appropriate even in patients without Wernicke's encephalopathy, refeeding syndrome, and cardiovascular complications? And there is no mention of what types of supplies are supplied every day. 3. Patients with diseases that can cause cognitive dysfunction such as stroke are not included in the study. But do patients who take brain function improvers without these diseases are excluded? 4. Are there any criteria for MoCA, MMSE and ADAS-Cog score that are excluded from the study because cognitive function is poor during the study period and neurological evaluation or treatment is required?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dr. Ertugrul Erken, Kahramanmaras Sutcu Imam Universitesi
Comments to the Author:

- This study aims to evaluate the effects of combined thiamine and folic acid treatment on cognitive functions in chronic hemodialysis patients. This is the study protocol of a prospective, randomized, placebo-controlled trial. The research question is clearly outlined. The researchers have also done a pilot study to determine their study goals and the sample size. This manuscript is the detailed methodology of a multi-ceter study. Therfore, the results of the current study are not included. According to the literature it may be wise to make a 1 point decrease in the MoCA cutoff values in this specific study population. This study (when finished) may lead to very interesting, scientific and valuable results.
Thank you for your important comments and suggestions on this research protocol, and we will consider to make a 1 point decrease in the MoCA cutoff values in this specific study population.
Reviewer 2
Dr. Yi-Lung Chen, Chang Gung Memorial Hospital
Comments to the Author:
- This manuscript conducted a randomized, placebo-controlled, double-blind study to examine Thiamine and folic acid in the treatment of cognitive impairment in maintenance hemodialysis. This is an important issue and the most study design in this study is adequate. I have some suggestions to authors for improving their study design and presentation.
- The full name of Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) should be spelled out when it first occurred in this manuscript.
Thanks for this important suggestion, we revised it in the text.
- Some grammar tense is not consistent in this manuscript. For example, " Even if the subject is unable to return to the study center for visits, the investigator will complete all available data on the Case Report Form (CRF) and record the reason.." and " It will be listed separately that the number of subjects selected…"But in their discussion, "The subjects were randomly divided into treatment group… The authors should consider the English editing for their manuscript."
Thank you for pointing out the grammatical errors in our manuscript. We have revised them in the text.
- The DPI of their Figure 1 is too low, please provide a better solation of a new Figure, with DPI at least 300, or 600 which is even better.
Thanks for your suggestion, we have provided a higher DPI of Figure 1.
- For the statistics, some more corrected analytical strategies can be used in this study. First, the authors mentioned within comparison and between comparison using repeated measure ANOVA, and simple oneway ANOVA. However, I think the generalized estimating equations (GEE) can be more powerful to analyze their data. Second, authors mentioned that Kaplan-Meier survival curve was used for survival analysis. However, the endpoints the authors used were ADAS-Cog score, serum thiamine, folate, and homocysteine level, cranial functional magnetic resonance imaging, and prognosis. I cannot see any binary variable for survival analysis. Please specify the outcomes they want to use for survival analysis.
Thank you for your important suggestion on statistical methodology for this study. First, according to your suggestion, we have added GEE to analyze the data of within comparison and between comparison. Second, we revised the secondary endpoints 3 to “survival comparison between treatment group and control group at 96 weeks of follow-up.” We would like to observe if there will be a survival benefit with thiamine and folic acid at 96 weeks of follow-up.

Reviewer 3
Dr. Seun Deuk Hwang, Inha University Hospital
Comments to the Author:
- This study enrolled patients with MoCA scores below the standard. However, is it not good to use the ADAS-Cog score, which is the primary endpoint, instead of using the MoCA score when enrolling patients with the ADAS-Cog score for the primary endpoint? Of course, the MoCA score is also finally obtained, but is it good to predict and evaluate the patient's cognitive impairment prediction and response when the enrolled index and the primary endpoint index are different?

Thank you for pointing out this important question. Actually, we did use MoCA scores as the primary endpoint to determine whether cognitive function improved in the pilot study [Lu R, Xu C, Li Y, Yu L, Shao X, Xie K, et al. The Incidence Prognosis and Risk Factors of Cognitive Impairment in Maintenance Haemodialysis Patients. Blood Purification. 2019;47,:101-108.]. However, when the pilot study results were submitted, some reviewers of neurologists proposed an important point: MoCA score [Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53:695-699.] was only used for the diagnosis of cognitive impairment in patients including hemodialysis patients, however, the internationally recognized method to determine whether cognitive function improved is ADAS-Cog score [Mohs RC, Rosen WG, Davis KL. The Alzheimer's disease assessment scale: an instrument for assessing treatment efficacy. Psychopharmacol Bull. 1983; 19(3):448-450.] after drug intervention. Therefore, we adopted MoCA score as the eligibility criteria and ADAS-Cog score as the primary endpoint in this study.

- Is the amount of thiamine and folic acid mentioned in the study appropriate even in patients without Wernicke's encephalopathy, refeeding syndrome, and cardiovascular complications? And there is no mention of what types of supplies are supplied every day.

In fact, with regard to the dosage of thiamine and folic acid, we are also exploring. In addition to the experience in Wernicke's encephalopathy, refeeding syndrome, and cardiovascular complications, We based on the results of our pilot study (improvement in MoCA score and reduction in adverse events in the treatment group with this dose) as the basis for setting the dosage in this study protocol. It may be necessary to set different groups of therapeutic dose to determine the appropriate therapeutic dose in the future.

Moreover, the types of supplies are as follows: thiamine and folic acid are taken orally in tablets, which are supplemented in detail in the text. Thanks.

- Patients with diseases that can cause cognitive dysfunction such as stroke are not included in the study. But do patients who take brain function improvers without these diseases are excluded?

Thank you for your comments. Since the placebo control was used in this study, subjects taking brain function improvement drugs were not excluded in order to reflect the principle of patient benefit first in GCP.

- Are there any criteria for MoCA, MMSE and ADAS-Cog score that are excluded from the study because cognitive function is poor during the study period and neurological evaluation or treatment is required?

The study did not specifically include deterioration of cognitive function during follow-up as an exit criterion for the following reasons:

1.In this study, subjects with MoCA score less than 26 will be selected, and most of them have mild or moderate cognitive impairment. Due to the slow development of cognitive impairment, except for serious adverse event such as cerebrovascular accident, subjects will not rapidly deteriorate to the point of withdrawal from the study during the 96-week follow-up according to clinical experience.

2.When a serious adverse event, such as a cerebrovascular accident, causes rapid deterioration of cognitive function, the investigator may decide whether to withdraw the subject from the study, which is mentioned in the withdrawal criteria in the protocol.

We reorganized all the modifications are marked in yellow. We deeply appreciate your consideration of our manuscript, and we look forward to receiving comments. If you have any queries, please don't hesitate to contact us.

Thank you and best regards,

VERSION 2 – REVIEW

REVIEWER	Erken, Ertugrul Kahramanmaras Sutcu Imam Universitesi, Nephrology
REVIEW RETURNED	04-Sep-2021

GENERAL COMMENTS	The revision is clear and satisfactory.

REVIEWER	Chen, Yi-Lung Chang Gung Memorial Hospital
REVIEW RETURNED	18-Sep-2021

GENERAL COMMENTS	I am satisfied with the authors' reply and have no further comment.