Author’s response to reviews

Title: Efficacy of N,N'bis-(2-mercaptoethyl)isophthalamide on mercury intoxication: A randomized controlled trial

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Author’s response to reviews:

Dear reviewers,

thank you very much for your thorough revision and helping greatly to improve this manuscript! I revised the language and restructured the manuscript according to your annotations.

In the following section I will answer your questions and comment your remarks, starting with reviewer #1:

line 104-110

Discretionary revision - I included the numbers of the individuals according to your suggestion

line 128-134

Major revision - I included a short explanation of the exposure and picked the topic up in the discussion. As you pointed out, it is indeed a problem.
Minor revisions - I deleted the total fatigue score from the manuscript

I restructured and overhauled the tables.

"You use the Wilcoxon test to compare two independent samples (treatment group with placebo group) - I think the correct test would be a t-test if data are normally distributed or a Mann-Whitney non-parametrical test for such a comparison. The Wilcoxon test you can use to compare the same group (same sample) before an after treatment, which is also relevant for you as you can compare the test results within the same group at baseline with the results at day 15 and with day 45 to see if any significant change has occurred. Or if normally distributed you can use the paired t-test."

This is a problem of naming: Mann-Whitney test has several names and in SAS it appears as Wilcoxon two-sample test, which can easily be confused with the Wilcoxon signed rank test. Therefore I renamed it in the manuscript.

Results

I harmonized the table names, they are now consistent, please see the text. The tables were simplified and I included the BMI.

"In all tables 1-3 I miss the p-values to see the significant differences between the three groups."

I discussed this with our statistician and he concluded that adding p-values to show a difference in baseline characteristics between groups are from a statistical point of view not logical in a randomized study. Such significance tests assess the probability that observed baseline differences could have occurred by chance given the data; however, we already know that any differences seen in the baseline characteristics are caused by chance since the study is
randomized. Therefore, I didn't include the p-values to the baseline data, however, I am happy to provide the values to you, if you don't agree.

line 306-474

Major revision I changed the tables as you suggested and moved the individual MIS items to the appendix.

line 440-442 Please see the text.

Table 5 I added the p-values

Discussion

line 483-484

Minor revision - Please see the text

Major revision - I added a section about the treatment effects.

Major revision - I added a section concerning the strength and limitations.

I am confident that you agree with the changes.

Reviewer #2:

"Do not repeat detailed results in the text which are presented in the tables. It is complicated and the reader is lost in details. E.g., prefer <0.05, <0.01, <0.001 and not significant for the p-value in the text rather than the exact value."

I simplified the result section according to your suggestions.
"Chapter "Mental and physical fatigue score" contains too many information. Suggestion: delete the information about the changes of the points."

I delete the information about the changes and the section with the total fatigue score.

"The discussion should be more extensive..."

I added two sections about the exposure and the strengths and limitations.

line 537ff: "The optimal dose in relation to the body weight should be ascertained to safe resources."

This is true for patient reatment but not applicable in a study at this early stage as positive effects need to be proven first and then quantified.

line 330f and line 345f: "Discuss it."

This section was moved to the appendix and therefore is not discussed.

line 535: "The sentence could be changed; e.g.: In future studies, the dose of the product should be adapted to the workers body weight."

Please see the text

"The amendments of the protocol are confusing. Please try to reduce this information."

I deleted most of the sections about the amendment as they are not very relevant for the results.

"Please mention the sample size in the abstract."

Please see the text
"I recommend moving the text from lines 74 to 82 on page 5 into line 65 on page 4." I did as you suggested.

"Figure 1 is not mentioned in the text." It is now in the background section.

I delete all pointed out repetitions, unclear formulations and moved the section as you suggested.

"Table 1: The rows for "Sex" and "Ethnic Origin" can be deleted. Mention it in the text." Please see the table.

"Table 2: The rows titled with "No" can be deleted."

I deleted them.

"line 308: "...the majority of..." all participants or all treated participants?"

I clarified it in the text.

"line 318: 0.19 for which group?"

Please see the text.

- line 374f: "...in all treatment groups" or "...in both treatment and the placebo group"?

The second. Please see the text.

"line 399f: The chapter should not start with the information about similar results of the sensitivity analysis. Remove it to the end of the chapter or even to the end of each topic."

I followed the suggestion.
- Table 4: I changed the table and added an explanation to the section text and a footnote

"line 441: I do not understand how a value below 0 is possible."

This describes the change in the score, the negative value means the condition of the participants got better. The LSMean are the according to the model adjusted means

- Table 5: "I do not understand the columns "Change from baseline" "Median", "Min", "Max"."

Please see the changed table and the explanatory text

line 139: "randomization was done in blocks of six". I do not understand."

I rephrased it

"Figure 2: Please define "*Amd. No. 3". Please clarify the brackets in the box "Inclusion". If 12 subjects were screened on protocol version 4.0, how is it possible to include 17?"

It was deleted from the figure as it is misleading.

Thank you both very much for your work and time to improve this manuscript

Best regards,

Paul Schutzmeier