Author's response to reviews

Title: PISA. The effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute stroke: Protocol for a phase II double-blind randomised placebo-controlled trial

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General:

Dear editor,

All changes in the manuscript are marked yellow.

We changed the title to
"PISA. The effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute stroke: Protocol for a phase II double-blind randomised placebo-controlled trial", as you suggested. It is indeed the case that our protocol has already been approved by the medical ethics committee in the three participating centers. At this moment, we have concluded the follow-up of the last patient and we are ready to carry out the final statistical analysis of the data.

We added references to two small clinical trials of paracetamol in acute stroke patients (published after submission of this manuscript) in the background section.

We thank both reviewers for their helpful comments.

Reviewer 1:

1. Regrettably, our medical ethics committee ruled that we should go into a lengthy and time-consuming national procedure to obtain approval for a trial that used consent by proxy. For this phase II study we decided to solve the dilemma by excluding patients with severe aphasia.
2. Investigators were advised not to include patients with a clinical diagnosis of chronic liver failure, patients with a history of alcohol abuse or AST, ALT, AF, or patients with total bilirubin levels exceeding twice the local upper limit of normal.
3. We were aware of the dangers of treatment with high dose paracetamol. In the previous study we conducted, we had similar inclusion and exclusion criteria. The number of patients with liver function disturbances was not increased in the paracetamol group.

4. Our primary outcome is body temperature at 24 hours after start of treatment. We expect more than 90% compliance in this period. We need only 2 extra patients per treatment arm to compensate for lost patients. The three-month follow will not be complete, as patients will die and become lost, but this study is not powered to find a difference in three-month outcome anyway. We put more emphasis on this point the methods section.

5. This is an important point. In our view, randomizing stroke patients with body temperatures over 38 C to placebo or antipyretic treatment is not unethical, because we do not know at all if treating fever improves outcome. Actually, it may even cause harm, because lowering fever means that important information concerning the presence and course of infectious disease will be lost. Treating fever may improve well-being in individual cases, and therefore we leave it to the discretion of the treating physician whether, when and how antipyretic treatment should be started. We added a comment concerning this point to the section on safety concerns.

Reviewer 2.

1. In the section that describes the analysis, we added that the main analysis of the trial results will be done according to the intent to treat principle, but an "on treatment analysis" will be provided also.

2. We reread the CONSORT statement. We will follow it closely when we will report the results of this trial.

3. We argued in the background section, and more elaborately in the second paragraph of the discussion that a small reduction of body temperature in the acute phase of ischemic stroke may be beneficial. A large phase III study will be necessary to study functional outcome, which is -we agree- more "patient-relevant".