Reviewer's report

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

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Reviewer: Prof Jose Ferro

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Accept after discretionary revisions

PISA is an important well-designed trial comparing the efficacy of ibuprofen, high dose paracetamol and placebo in patients with acute ischaemic stroke. I have only a few suggestions concerning safety and the use of placebo.

1. Why are aphasics excluded? A proxy can give the informed consent.

2. Laboratory criteria for liver failure. Indicate the upper limits of AST, ALT, GGT accepted (5x the normal upper limit?) for inclusion.

3. Because of the risk of hepatic toxicity and GI bleeding I suggest an intermediate laboratorial assessment at day 3.

4. Sample size. I suggest rounding the number to 30 for each arm, in order to retain power for the on-treatment analysis. Some patients will stop the trial medication and others will die before the end of the trial.

5. Ethical problems with the use of placebo. I have strong concerns with the use of placebo in patients who are febrile, because they are denied the best available pharmacological treatment. Fever produces at least discomfort to the patient. My recommendation is to randomise patients with >38o only between paracetamol and ibuprofen.

Competing interests:

None declared.