Reviewer's report

Title: Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke. PISA, a phase II double blind randomized placebo-controlled trial. ISRCTN 98608690

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Reviewer: Dr Elmer Villanueva

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Overall Report:
Authors should be congratulated for progressing their original idea in a rigorous manner. The burden of disease of stroke and its consequences is immense and management options need to be elucidated. This study adds to the effort by clarifying specific issues and uncovering others for future research.

Specific Comments:
1. Abstract
a. Methods: The authors need to clarify how long after the diagnosis of stroke was made were the interventions given. [COMPULSARY]
b. Results: Add phrase: "Acetaminophen had no... subsequent four days [compared to placebo], and ibuprofen..."

2. Methods
a. Design: "Our study...". Consider "three-arm" instead of "three-armed".
b. Design: "...a CT scan that was...". Expand abbreviation on first use.
c. Design: "Patients with a posterior...". Omit "a".
d. Design: "...were not included, because occasional". Omit comma.
e. Design: "NIH Stroke Scale (NIHSS), [21] because...". Omit comma.
f. Design: "The NIH stroke scale was used to assess...". Capitalise first letters of "stroke scale".
g. Design: "...creatinine, liver functions, and CRP." Consider "...creatinine, liver function tests, and c-reactive protein (CRP)."
h. Design: "Body temperature was measured with a tympanic thermometer...". This issue is confusing because other places in the text refer to the use of rectal temperatures. The authors need to clarify how temperature was measured and how discrepancies between modes of measurement were resolved.
i. Study medication: "The first gift of medication...". Define "gift".

j. Randomisation and blinding: Allocation concealment must be described.

k. Adverse events: "...liver function disturbance (ASAT, ALAT, AF, or...". Expand abbreviation on first use. Yes, these are listed in the Abbreviations Section, but define them in the text so the reader's attention is not diverted to other sections needlessly.

l. Adverse events: "...serious adverse events on a two-weekly basis.". Consider "fortnightly" instead of "two-weekly".

m. Outcomes: The authors must clarify the reason for the two different methods of temperature measurement. They have to explain whether there are any differences between the two methods. If so, what they are and how much of an impact they have on the final outcome. How were secondary end points measured (rectally or tympanically)?

n. Outcomes: The authors must explain the significance of the area under the curve. What does it represent? Is it a valid and reliable end-point in the tracking of body temperature changes over time?

o. Outcomes: The authors have to define what the Rankin Scale and Barthel Index measure. Functional outcome has many meanings. Being specific will allow the reader to put into perspective the results.

p. Statistical analysis: The authors have to justify the use of multiple linear regression if randomisation has been performed. Why adjust if there are no differences during baseline? Specify which of the results (tables, graphs) report adjusted estimates. What covariates were used in the adjustment? Did the authors allow for the use of adjusted estimates in the estimation of sample size?

q. Statistical analysis: Power is 1-beta, not 1-2(beta).

3. Results

a. Baseline characteristics: "...related to increased body temperature were evenly distributed...". This does not seem to be the case. AF is 6-7 times more likely in those receiving active therapies, etc. Consider revising the statement for accuracy.

b. Patient flow: The text does not match the Figure 1. For instance, the text states that 8 patients stopped therapy; in the figure, only 6 are shown. Consider adopting CONSORT suggestions and tracking patient flow according to study milestones instead of outcomes.

c. Outcome: "...occurred early and was consistent...". Define "consistent". How is a reader to take this interpretation? Consistent with other studies, consistently lower than placebo, consistent with our expectation, etc?

d. Outcome: "Body temperature measurements...". Consider starting new paragraph.

e. Outcome: "... available in 52 of the 75 patients." Clarify discrepancy with Figure 1.

f. Outcome: "... tended to be lower in all groups (Figure 2)." Do the authors mean "all active treatment groups"? Figure 2 seems to imply that the placebo group's temperatures were elevated.

g. Outcome: "... but these differences were not significant." The authors need to clarify the time frame of this comparison. The previous sentence suggests that this comparison after 24 hours of therapy, but Table 2 says that this is seen after 5 days. The point estimates in the text also do not agree with those in Table 2.

h. Outcome: "The comparison between...". Consider starting a new paragraph.

i. Adverse events: Consider reporting the treatment assignments of those experiencing adverse events, especially those that died. Consider specifying whether the adverse events were certainly, probably, possibly, or not related to therapy.

4. Discussion

a. Validity: low and loading doses of aspirin. Consider putting into the "design" or "study medication"
sections. [COMPULSARY]
b. Validity: "This could not have confounded...". This statement is opinion and has to be justified. [COMPULSARY]
c. Validity: "This could not have confounded...". Could the results have been biased? Since all patients received aspirin, comparative effects would still hold (assuming that the effect of aspirin is constant across all patients). However, since aspirin has an antipyretic effect, could the final point estimate have been shifted toward the null, thereby accounting for the lack of statistically significant differences? [COMPULSARY]
d. Consider talking about the limitations of the present study. [COMPULSARY]

5. List of abbreviations:
a. Consider alphabetising.

6. Tables
a. Table 1: Make title more descriptive.
b. Table 1: Use x-bar to signify the mean.
c. Table 1: Medians and IQR are not given throughout the table. The footnote should be modified. [COMPULSARY]
d. Table 1: Close parenthesis in cigarette smokers assigned to the ibuprofen group. [COMPULSARY]
e. Table 1: Footnote: "... in the treatment strata." Consider "treatment arms." [COMPULSARY]
f. Table 2: If adjustment was used, state in the title, not as a footnote. What were the results of the other adjustments? [COMPULSARY]
g. Table 2: Repeated use of the phrase "in degrees C" can be eliminated through the incorporation of the phrase in the title. [COMPULSARY]
h. Table 2: Difference with placebo in change in temperature at 24 hours should be negative. [COMPULSARY]
i. Table 2: Difference between ibuprofen and placebo is -0.2, not -0.1. Please confirm. [COMPULSARY]
j. Table 2: What does "N" mean in the Rankin and Barthel results? [COMPULSARY]

7. Figure legends
a. Figure 2: Specify whether these are changes from baseline or a differential. [COMPULSARY]
b. Figure 2: "...during the first week...". Do the authors mean "first day"? [COMPULSARY]

8. Figures:
a. Figure 1: The arrows between the secondary and tertiary outcomes are confusing. Clarify whether patient flow is cumulative. [COMPULSARY]
b. Figure 1: Consider adopting CONSORT suggestions. [COMPULSARY]
c. Figure 2: Y-axis has to be titled correctly. These are changes in body temperature. [COMPULSARY]

9. CONSORT items to be completed
a. Recruitment [COMPULSARY]
b. Numbers analysed [COMPULSARY]

Competing interests:

None declared.