Author's response to reviews

Title: Equal antipyretic effectiveness of oral and rectal acetaminophen: a randomized controlled trial [ISRCTN11886401]

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Author's response to reviews: see over
Dear Editor,

Thank you for your review of our manuscript and for the thoughtful comments of the kind reviewers. We have revised the manuscript so as to address the major and minor comments. In addition, kindly find below our response to each comment.

Title:

We have replaced the word "efficacy" in the title with the word "effectiveness" to reflect the "real life" situation of our subjects, especially in terms of antibiotic administration and previous antipyretic intake. This will also be more consistent with the intent-to-treat analysis performed in the study. We are grateful for the reviewers for alerting us to this issue.

Response to Dr. Karel Allegaert

Major comments:

1. Prior intake of antipyretics: We agree with the reviewer that stopping antipyretics prior to enrolment for a period of 8 hours only may be a potential bias. Ideally, we would have liked to keep all our subjects off-antipyretics for 24 hours. However, this is considered unethical to do if purely for the sake of a clinical trial. Since most of febrile children would be receiving antipyretics by the time they present to their physicians, and since we are interested in the "effectiveness" rather than the "efficacy" of the 3 different doses and preparations of acetaminophen, we elected to stop previous antipyretics for a reasonable period of 8 hours, thus mimicking a "real-life" situation where 6-8 hours is considered to be a regular dose interval for antipyretic administration. In addition, we anticipated that the randomization process will dilute the effect of this potential confounder by having equal distribution of subjects with previous antipyretic intake among the three groups. Indeed, the proportions of such subjects were not significantly different among the three arms of the study (Table 1). We have addressed this point in the discussion section as suggested by the reviewer.

2. Antibiotic intake: We could not withhold antibiotics when needed for obvious ethical reasons. Excluding subjects who are receiving antibiotics from the study would compromise the feasibility of the study in terms of recruiting enough patients within a reasonable time frame. In addition, we anticipated that this confounding effect will be neutralized by the randomization process which, in fact, distributed subjects receiving antibiotics equally among the three groups (Table 1). We also tried to recruit our subjects into the study as close as possible to the time of admission (within 12 hours) in order to minimize the potential confounding effect of antibiotics, since infection control and subsequent antipyresis are usually expected after 24-48 hours from
antibiotic initiation. We believe that the role played by antibiotics in the antipyretic responses of the three treatments is minimal for the above-mentioned reasons, especially that the study duration was a short six hours only. We have addressed this potential confounder in the revised discussion also.

3. Dose variability: We agree with the author that the higher the acetaminophen rectal dose, the longer the time to maximum antipyresis (Pearson Correlation Coefficient $r = 0.8; p = 0.000$). It is well-established that the absorption of rectal acetaminophen is slower with larger suppositories as compared to smaller ones, the size here reflecting the dose of the suppository. Actually when we planned on doing this study, we wanted to prove that oral acetaminophen results in faster antipyresis than rectal acetaminophen, in view of the slower absorption of the rectal preparations. This is why we chose our primary outcome to be the time to maximum antipyresis instead of any other outcome relating to antipyretic effectiveness. Though we have succeeded to administer the standard 15 mg/kg in the oral group and a close 14.1 mg/kg in the rectal low-dose, the dose in the rectal high-dose group varied between 12.5-43.4 mg/kg. This was mainly due to the subject who received a low-dose instead of the allocated high dose and who was kept for the intent to treat analysis. We have recalculated the mean and range of the rectal high-dose after excluding this subject and found them to be 33 and 27.1-43.4 mg/kg respectively. The smallest dose of 27.1 mg/kg in this group is much closer to the high-dose range than to the low-dose range. In addition, by excluding this subject and doing an "as-treated" analysis of the time to maximum antipyresis, we found similar results to the intent-to-treat analysis. We have commented on the variability in the rectal dose in the revised results section.

Minor comments:

1. Time until temperature < 38.5: We compared the time to fever reduction by at least 1°C among the three groups using one-way ANOVA and found no significant differences ($p = 0.13$). This analysis is added to the secondary outcomes.
2. Reference 4: corrected.
3. Study procedure: Sentence rephrased so as to reflect that the pharmacist who knew the treatment allocation of each patient was the one to prepare the drugs as stated.
4. Conclusions: The statement on generalizability has been moved to the last paragraph of the results.
5. Labels added to table and figure.
6. The word "efficacy" was replaced with "effectiveness" in the title and throughout the manuscript. We would appreciate any comments on typographical errors or wrong use of a term if present; especially that English is not our mother language.
7. Area under the curve (AUC) analysis: We believe that AUC will not give more information than two-way ANOVA repeated measures. However if the reviewer insists on this analysis, we will consult a statistician to perform it for us.
Response to Dr. Ran D Goldman

We thank Dr. Goldman for his valuable comments. Below please find our response to the points raised by the kind reviewer:

Major Comment:

Limitations, weaknesses and imprecision of the study results: We have elaborated on these issues in the third paragraph of “Discussion” section, page 13.

Minor comments:

1. We have obtained the oral consent of children aged 10 years or more since this was the age required by the IRB for obtaining assent of children involved in the trial. A statement to this fact is added to the methods section.
2. Care providers: The care providers were the primary physicians of the children whose names appear in the acknowledgement sections. There was one nurse dedicated to the care of each patient, which is the usual situation for inpatient care. Any nurse could have had the chance to take care of more than one subject in the study. The nurses, the primary physicians and the house staff were all blinded to the treatment allocation of the subjects since the drugs were prepared by the pharmacist and sent to the floor ready to be administered (kindly refer to our methods section).
3. The epidemiologist Dr H Tamim, who is a co-author on this study, generated the allocation sequence. She was not involved with subjects in the study in any way. Our research assistant enrolled the subjects but was not involved in drug administration or in outcome assessment and was unaware of the treatment allocation of subjects.
4. Yes, our statistician Dr Mahfoud, also a co-author on the study, was blinded to the treatment allocation of subjects. The analysis was performed without breaking the codes of treatment, which was later done by the principal investigator when all analyses were completed.
5. We did not attempt to assess the success of blinding directly whether by asking parents, physicians or house staff members. However, after the study had ended, we asked the nurses who administered the drugs whether they could guess which treatment was being administered to their patients and they stated that it was difficult to guess since the suppositories were very similar in size and shape.
6. The nurse assigned to the patient’s care was the one to administer all medications (kindly refer to the details in the methods/study procedure).
7. A standard deviation of one hour was extrapolated from the time to Cmax SD’s reported in the literature assessing the pharmacokinetics of rectal acetaminophen (Kindly refer to reference 5).
8. The subject’s nurse was the one to record the rectal temperature using one electronic thermometer with disposable covers for the sake of minimizing variability (kindly refer to methods/study procedure). We had 2 such thermometers: one at each of the participating hospitals. A statement to this fact has been added to the methods section.
9. We removed the SD of the median duration of fever and kept the range.
10. Hypothermia: we have defined hypothermia as a body temperature below 36.5° C rectally (definition appears in methods/statistical analyses and in results/secondary outcomes). We could not find another medical term to describe these abnormally low temperatures. Perhaps the kind reviewer can suggest another term!!

11. The word “presentations” is now replaced with “preparations”.

12. Conclusions section has been shortened. The paragraph relating to generalizability has been repositioned in the results section.
Response to Dr. Diederik Dippel

We thank Dr. Dippel for his thoughtful comments and suggestions. Below kindly find our response to each point raised by the reviewer:

Major comments:

1. Treatment effect as a difference in mean temperature with the reference treatment: This is basically the analysis that we have reported using two-way ANOVA which compares the mean change in temperature from baseline at each hour, the result of which was not significantly different among the three groups. In addition, we did report the mean and the 95% CI of the primary outcome and have added now the mean and 95% CI of another secondary outcome: the time to fever reduction by at least one degree. Looking at all studied outcomes, the ones reported by us and the ones suggested by the reviewers, we could not find significant differences among the three treatment groups. Hence our conclusion that the three treatments have similar antipyretic effects may be justified.

Minor comments:

1. We have rephrased the sentence on hypothermia from “more incidence of hypothermia..” to “may result in hypothermia” and removed the term “random list”. The word “Epstein” now replaces “Ebstein”. We would appreciate if the reviewer could alert us to any other terms that need rephrasing since English is not our mother language.

Discretionary revisions:

1. Primary outcome: In view of the well-established faster absorption of oral acetaminophen as compared to rectal acetaminophen, we chose our primary outcome to be the time to maximum antipyresis expecting that the oral group would have a significantly shorter time to maximum temperature reduction, as compared to the other two groups. We also believed that it makes sense in real clinical life since parents’ main concern is usually how to drop the child’s fever quickly. As for the time to fever reduction, we have added another secondary outcome to our analyses: time to fever reduction by at least 1°C, which was also not different among the three groups.

2. Your concern about the high dose group receiving a potentially high dose is well-justified. We have encountered similar concerns at the time of our study proposal submission from the Research Committee/IRB and our colleagues in the Pediatrics department. These concerns actually made us lower the rectal high-dose from 40 mg/kg to 35 mg/kg. To address your concerns, there is a substantial literature on the use of high dose rectal acetaminophen in the literature that investigated acetaminophen analgesic effects (dose reaching up to 45 mg/kg). The studies suggest that high-dose rectal acetaminophen is

Finally, we would like to thank the reviewers for their valuable comments which we believe improved our manuscript. We would also like to thank BMC Pediatrics for considering our manuscript for publication. We hope that our response to the points that were raised by the kind reviewers meet your expectations and look forward to hearing your decision on publication.

Sincerely,

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