Reservations about the eClinicalMedicine report of a novel glucose-free amino acid oral rehydration solution

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eClinicalMedicine 2025;81: 103110
Published Online xxx
https://doi.org/10.1016/j.eclinm.2025.103110

We read with interest the report by Bardhan and colleagues that report results of a trial comparing an amino acid-based oral rehydration solution (ORS) with the standard World Health Organization (WHO) ORS.[1] The authors conclude that the results "support the non-inferiority" of the experimental solution. There are aspects of the trial as reported that lead us to question this conclusion. Full disclosure that many of the authors are our friends and/or colleagues, but in the interest of the scientific process we prefer to raise the following questions in a public rather than private dialogue.

Rationale for this ORS formulation

There is much unreferenced emphasis in the Introduction and Discussion on the need and benefits of a non-glucose ORS for which no references are cited to support. For example, it is stated that glucose-containing ORS "is an obstacle impeding ORS uptake". The authors are quite right that interventions to increase ORS uptake are needed, but we are unaware of evidence to indicate glucose is a constraint. We similarly question that glucose-free ORS has "great utility" where obesity and insulin resistance are prevalent. Consumption of the quantity of glucose in an ORS formulation for a few days for acute diarrhea is unlikely to have an impact on the prevention of obesity or the consequences of insulin resistance. And while it is stated that study results alleviate concern that a non-glucose ORS might result in hypoglycemia, the risk of hypoglycemia is practically zero in non-severely malnourished children with acute diarrhea who are also consuming human milk and/or food (as has long been the recommendation of WHO, AAP and other recommending bodies).

Claims of non-inferiority

The published trial protocol[2] specifies that the study is a superiority rather than non-inferiority trial. The Background states the aim was "to know whether [the experimental ORS] will be superior or not to WHO-ORS" and the Aims (twice) and Study Design sections state that the study is a "superiority trial". The authors report multiple outcomes in the trial as not significantly different ($p < .05$ was the stated level of significance) between participants who received the experimental ORS vs. the WHO-ORS, including duration of diarrhea, stool output, urine output, body weight, and several biochemical outcomes. Neither the published protocol nor the clinical trials listing (NCT04677296) refers to non-inferiority margins or the justification, but the trial report introduces the concept of non-inferiority in the Methods section ("non-inferiority was likewise considered using a predefined non-inferiority delta of 20% of the reference product"). This distinction is important as non-inferiority trials require substantially different approaches in design, analysis, and interpretation compared with superiority trials and as has been noted, "Noninferiority cannot be established on the basis of the absence of a significant difference between treatments in a superiority study."[3]

Differential loss to follow-up

Figure 1 notes that 36 participants in the experimental group were excluded from analysis due to "major deviations" (vs. none in the WHO-ORS arm). This is 25% of those who were randomized to this study arm and no elaboration or explanation is offered in the Discussion or elsewhere. It appears to call into question whether the experimental ORS can be readily or practically implemented.

Funding source and author responsibilities

The industry funders were reported to have "had no role in study design, conduct of the study, data collection or management of the study" but four co-authors including the corresponding author for the report are affiliated

DOI of original article: https://doi.org/10.1016/j.eclinm.2024.102630
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with the sponsor Extrinsic Bioscience. Based on ICJME guidelines, it seems likely that these authors made substantial contributions to the design of the trial, or acquisition or analysis of the data.

Despite substantial reductions in diarrheal deaths by more than 80% since 1980,[4] diarrheal diseases continue to cause substantial morbidity and growth faltering among the world's children[5]; sound clinical trial science is fundamental to improve therapies for them.

Contributors

Both Dr. Fuchs and Dr. Santosham conceptualized and wrote the original draft and writing, review, and editing of the letter.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships other than those declared in the opening paragraph that could have appeared to influence the work reported in this paper.

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