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Ringer's Lactate or Normal Saline for Children with Severe Dehydration: Change-from-baseline Analysis *vs* 'Conventional' ANCOVA

We read with interest the results of the randomized trial on Ringer's lactate (RL) *vs* normal saline in children with acute diarrhea and severe dehydration [1]. The study authors had used a rigorous methodology to address a pertinent question, and found no difference in the outcomes between the two groups. We wish to highlight a few methodological issues, which, if addressed, could have further improved the quality of the study:

The authors mention that the primary outcome variable was 'change in pH from baseline'. However, they possibly used the difference in *post-intervention* pH between the groups and not the magnitude of 'change from baseline' for calculating the sample size. There is no mention of the mean or SD of the change in pH from baseline in the study from which the authors estimated the sample size. The sample size could have been very different if the standard deviation of this outcome was large (or small!) from the one used in the sample size calculation.

At least four different approaches can be employed to analyze a continuous outcome that is measured at two time points (*i.e.* baseline and after treatment) in a RCT: post-treatment, change between baseline and post-treatment, percentage change between baseline and post-treatment, and analysis of covariance (ANCOVA) with baseline value as a covariate [2]. The authors chose to use a slightly different approach using the change from baseline as the outcome but used ANCOVA to adjust for a few covariates other than the baseline pH. Compared to the change from baseline analysis, ANCOVA with baseline as the covariate has higher statistical power, particularly if correlation coefficient between baseline and follow-up values is <0.8 [2,3]. More importantly, the latter analysis has the advantage of being unaffected by baseline differences between the groups (it adjusts each patient's follow up score for his/her baseline score) [3]. In contrast, the change from baseline analysis takes the pretest difference too seriously and might produce biased results in the presence of imbalance in baseline scores between the two groups [4]. Though not statistically significant, the baseline pH was higher in the RL group [1].

Instead of providing only the *P* value, the authors should have provided the results of the 'ANCOVA' model in a more detailed way - Vickers, *et al.* [3] have provided an excellent model for depicting the results of the analysis using ANCOVA model (albeit, with baseline as covariate). The unadjusted and adjusted mean difference of change from baseline along with 95% CI would have given the readers some idea about the precision of the results and the magnitude of confounding caused by the two covariates.

The term 'repeated measures' usually implies that the analysis involved an interaction term, i.e. 'group*time' in the model. It is not clear if the *P* value mentioned in the study refers to the *P* value of this interaction term.

The authors adjusted only for baseline serum sodium and chloride - the two factors found to be significant on bivariate analysis - in the ANCOVA model. Many researchers have effectively demonstrated the inappropriateness of this approach, *i.e.* adjustment for only 'significant' variables [5]. Moreover, the clinical relevance of adjusting for serum chloride when baseline serum pH had already been accounted for in the change from baseline analysis is not clear. The better approach would be to use pre-specified ANCOVA where a few *a priori* selected important baseline variables are used as covariates [6]. An important variable that had to be adjusted was the time interval between the baseline and the time to achieve primary end point, as the latter was not fixed in the two groups. Not including it in the model because of lack of significant result is not valid as the

insignificant result is more likely be due to lack of power rather than due to true absence of difference between the groups.

M JEEVA SANKAR AND *MANI KALAIVANI
Newborn Health Knowledge Center (NHKC)
WHO Collaborating Centre for
Training & Research in Newborn Care
*Departments of Pediatrics and *Biostatistics,*
AIIMS, New Delhi, India -110029
jeevasankar@gmail.com

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Preventing Paracetamol Overdose in Children: Do We Really Need a 500 mg/5mL Preparation?

Although the safety profile of paracetamol compared to other analgesics is excellent, acute overdosage and therapeutic excesses are commonly recognized problems [1]. The recommended dose of paracetamol is 10-15 mg/kg/dose and not exceeding 60 mg/kg/day [2]. In the United Kingdom legislations have been introduced to restrict the pack size of acetaminophen tablets that is available for sale. Its impact on reducing acetaminophen toxicity is yet to be determined convincingly as few studies indicate a reduction in number of fatal cases of toxicity and reduction in hospitalizations to liver units, whereas some studies indicate that there has actually been an increase in the number of cases [3].

In India, it is surprising to find that the drug controller of India has approved a formulation for oral paracetamol suspension having strength of 500mg/5ml by a reputed Indian company specializing in different paracetamol dose preparations. Is there a percieved need to have such a preparation? In our opinion It is likely to cause more confusion and more chances of drug overdosage by the unassuming lay public if purchased over the counter for self medication. Having such a preparation at home, especially without child resistant caps could also lead to unintentional poisonings among infants and young children. For an infant weighing ten kilograms, an acute intake of as low as ten milliliters of the preparation may prove fatal. There is no justification for its use whatsoever as syrups or suspensions are costlier than tablets and most children as well as majority of caregivers prefer tablets over syrups or suspensions [4]. Hence there is an urgent need to rethink on the need for introducing such formulations and to withhold licensing of such formulations in future considering its potential for causing overdosage and toxicity.

***V SOMA AND C VENKATESH**
Department of Pediatrics,
Mahatma Gandhi Medical College & Research Institute,
Pillaiyarkuppam; and
cvenkatesh@hotmail.com
**Consultant Pediatrician; Puducherry,*

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