Non-Glucose Oral Rehydration Solution – Does it Make a Good Thing Better?

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Diarrheal disease continues to be a significant burden in terms of childhood morbidity and mortality despite tremendous progress in many fields. The 2007 Indian Academy of Pediatrics guidelines on management of acute diarrhea(1) emphasized three points: (*i*) low-osmolarity oral rehydration solution (ORS) is the universal rehydration solution for all ages and types of diarrhea; (*ii*) oral zinc therapy is recommended in all types of diarrhea; and (*iii*) probiotics and antisecretory agents are not recommended based on current knowledge. These guidelines are in line with preceding WHO recommendations(2) and based on robust evidence. Feasibility of implementation in routine practice makes it the cornerstone of management in our country.

The question is whether low-osmolarity ORS can achieve even better results by changing its composition. Addition or replacement with amino-acid (glycine/alanine) in ORS showed promise some years back, but has not been shown to be useful. Rice and other cereal based solutions release glucose very slowly, not only increasing the reabsorption of water and electrolyte(3), but reducing the osmotic load as well. If this slower process could translate into reduced stool losses and/or shorten the duration of diarrhea, it would make a good thing even better. This issue is explored here.

RELEVANCE

There is little doubt that the clinical problem (diarrheal dehydration), population (children, especially those under five years old) and intervention (non-glucose based ORS) are highly relevant in the context of our country; owing to high overall diarrheal disease burden, frequent occurrence of dehydration, ease of administration of ORS, acceptability of oral rehydration among physicians and the community in general, and strong commitment of the Government and international agencies to tackle the problem(4-6). The relevant outcomes of interest are mortality, hospitalization, treatment failure (need for administration of intravenous fluid), duration and/or amount of diarrheal losses, complications related to diarrhea and/or dehydration, adverse events related to ORS and cost of therapy. Thus the clinical question is: "*In children with diarrheal dehydration (population), does non-glucose oral rehydration solution (intervention) result in better clinical outcome (outcome) as compared to low osmolarity glucose ORS (comparison)*"

CURRENT BEST EVIDENCE AND CRITICAL APPRAISAL

An updated Cochrane Library search on 24 April 2009, with the term '*diarrhea*' yielded 21 Cochrane publications (including 8 protocols for systematic reviews) and 31 other systematic reviews; '*gastroenteritis*' yielded two Cochrane reviews and 5 other systematic reviews. Among these, one Cochrane review published 10 days back(7) compared polymer-based (rice, wheat etc) ORS against glucose-based ORS in adults and children. The authors reported that polymer-based ORS was superior in terms of reduced need for intravenous

infusion, shorter duration of cholera diarrhea, lower stool output and comparable rate of adverse events. However, careful appraisal of the data reveals that the authors reported their findings, combining data of standard (310 mOsm/L) ORS and low osmolarity ORS (<270 mOsm/L) in the control group. Although a sub-group analysis of low-osmolarity ORS trials was done, adult and pediatric data were combined to get the pooled estimate. As standard ORS is no longer the recommended rehydrating solution and combining pediatric with adult data is inappropriate, the conclusions of the Cochrane review cannot be taken at face value.

Therefore, a fresh systematic review was undertaken comparing low-osmolarity glucose ORS versus non-glucose ORS with the same electrolye composition. For this, Pubmed was searched on 25 April 2009 using the terms '*diarrhea* AND *systematic review*' (Limits: all child) yielding 352 citations; another search using "*oral rehydration*" (Limits: randomized controlled trials, all child) yielded 64 citations. A third search beyond the date of the Cochrane review search (September 2008) with the term "*ORS*" (Limits: All child, randomized controlled trials) yielded 2 citations. Sixteen trials from these searches were considered relevant; from these 13 were excluded. Three trials from the Pubmed search and one additional trial from the Cochrane review comprise current best evidence on the subject. ***Table* I** summarises the characteristics of included(8-11) and excluded trials(12-24).

The four included trials can be regarded as having average methodological quality. All of them used appropriate randomization, though only one reported allocation concealment(11). None of the trials blinded observers or participants; all included

TABLE I CHARACTERISTICS OF INCLUDED AND EXCLUDED RANDOMIZED CONTROLLED TRIALS

Included trial	Participants	N	Interventions
Iyngkaran 1998 (8)	<6mo old with acute diarrhea (<7 days)	63	Rice-based ORS (n=31) *vs* glucose-based ORS (*n*=32)
Nanulescu 1999(9)	1-12mo old with acute watery diarrhea and mild to moderate dehydration	113	Rice-based ORS (n=48) *vs* glucose-based ORS (*n*=51)
Dutta 2000(10)	2-10 y old with *V. cholerae* acute watery diarrhea with severe dehydration	58	Rice-based ORS (*n*=19) *vs* glucose-based ORS (*n*=19)
Maulen-Radovan 2004(11)	3-24 mo old with dehydration	189	Rice-based ORS (n=97) *vs* glucose-based ORS (*n*=92)

Excluded Trials	*Reason for exclusion*
Khin-Maung-U 1991(12)	Additional amino acid present in non-glucose ORS
Grange 1992(13)	Additional amino acid present in non-glucose ORS
Sabchareon 1992(14)	Both ORS did not have the same electrolyte composition
Murphy 1996(15)	Electrolyte composition of ORS not specified
Ibrahim 1997(16)	Comparison of two non-glucose ORS
Akosa 2000(17)	Comparison of two non-glucose ORS
Alam 2000(18)	Intervention consisted of addition of non-glucose polymer to ORS
Zaman 2001(19)	Comparison not with glucose-based ORS
Hoekstra 2004(20)	Intervention was not a non-glucose polymer ORS
Raghupathy 2006(21)	Intervention consisted of addition of non-glucose polymer to ORS
Gutierrez 2007(22)	Intervention was not a non-glucose polymer ORS
Zavaleta 2007(23)	Both ORS did not have the same electrolyte composition
Alam 2008(24)	Intervention consisted of addition of non-glucose polymer to ORS.

EURECA CONCLUSION IN THE INDIAN CONTEXT

- Non-glucose low osmolarity ORS is not superior to low osmolarity glucose ORS, despite statistically significant superiority for some outcomes.

around 90% or greater of randomized participants in the analysis.

The results are summarized in ***Table* II**. None of the trials examined mortality or hospitalization as an outcome. Non-glucose ORS was comparable to glucose ORS in terms of treatment failure (requirement of intravenous fluid), as well as the frequency of two adverse events *viz* vomiting and hyponatremia. Hyponatremia was surprisingly frequent in the single trial reporting it; this trial was conducted in children with cholera diarrhea having severe dehydration. This could be a matter of concern for using low osmolarity ORS (either type), if substantiated by other reports. The duration and amount of diarrhea were significantly reduced with non-glucose ORS. However, these statistically significant differences may not have as much clinical significance considering that the duration was shortened by only about 4.5 hours and the amount by less than 25g/kg, *i.e* 2.5% body weight, although the latter represents approximately 25% decrease compared to glucose ORS. It may be recalled that 5% loss results in mild dehydration in infants and young children (3% in older). Thus, it is difficult to agree with the Cochrane review conclusion that non-glucose ORS is superior, although both solutions can be considered comparable. Owing to limited data, no meaningful sub-group analysis based on age of participants, type of diarrhea, degree of dehydration or type of cereal in non-glucose ORS, could be performed.

EXTENDIBILITY

All the four included trials were conducted in developing countries including one in India. Diarrhea was defined by the usual clinical definition *viz* ≥3 watery stools per day. The clinical setting comprised different age groups, level of dehydration and type of diarrhea, all of which occur in Indian children. Two limitations of the current best evidence are that it is limited in terms of power (small sample size) and the four trials are heterogenous in terms of participants, degree of dehydration and outcomes assessed. Therefore, although the evidence can be extended to our clinical setting, it is unlikely to be the final word on the subject.

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TABLE II SYSTEMATIC REVIEW COMPARING LOW-OSMOLARITY NON-GLUCOSE ORS VERSUS LOW-OSMOLARITY GLUCOSE ORS

Outcome	Trials	Participants	Results	Interpretation
Mortality	0	–	–	–
Hospitalization	0	–	–	
Treatment failure	2	276	RR (95%CI): 0.44 (0.04-5.37)	Both groups similar
Duration of diarrhea (h)	2	137	WMD (95%CI): -4.5 (-7.2, -1.8)	Statistically significant, but limited clinical significance
Amount of diarrheal losses (g/kg)	1	99	WMD (95%CI): -24.6 (-40.7, -8.5)	
Complications	0	–	–	
Vomiting	1	63	RR (95%CI): 0.56 (0.24, 1.34)	Both groups similar
Hyponatremia	1	38	RR (95%CI): 0.67 (0.22, 1.99)	Both groups similar
Cost	0	–		

RR = Risk reduction, WMD = Weighted mean difference, CI = Confidence Interval

REFERENCES

1. Bhatnagar S, Lodha R, Choudhury P, Sachdev HPS, Shah N, Narayan S, *et al*. IAP Guidelines 2006 on management of acute diarrhea. Indian Pediatr 2007; 44: 384-389.
2. World Health Organization, Department of Child and Adolescent Health and Development. Clinical management of acute diarrhoea: WHO/UNICEF joint statement [WHO/FCH/CAH/04.7]. Geneva: World Health Organization; 2004.
3. Pizarro D, Posada G, Sandi L, Moran JR. Rice-based oral electrolyte solutions for management of infantile diarrhoea. New Engl J Med 1991; 324: 517-521.
4. World Health Organization. The World Health Report 2002: Reducing risks: promoting healthy life [WHO/WHR/02.1]. Geneva: World Health Organization; 2002.
5. World Health Organization. The World Health Report 2005: Make every mother and child count. Geneva: World Health Organization; 2005.
6. World Health Organization. The challenge of diarrhoeal and acute respiratory disease control. Point of Fact No 77. Geneva: World Health Organization; 1996: 1-4.
7. Gregorio GV, Gonzales MLM, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. Cochrane Database Syst Rev 2009; 2: CD006519.
8. Iyngkaran N, Yadev M. Rice-starch oral rehydration therapy in neonates and young infants. J Trop Pediatr 1998; 44: 199-203.
9. Nanulescu M, Popa M, Panta P, Butanariu A, Muresan M, Gocan S, *et al*. The efficacy of an oral-rice based electrolyte solution in infants with acute diarrhea as compared to a glucose-based electrolyte solution. Rom J Gastroenterol 1999; 8: 177-182.
10. Dutta D, Bhattacharya MK, Deb A, Sarkar D, Chatterjee A, Biswas A, *et al*. Evaluation of oral hypo-osmolar glucose-based and rice-based oral rehydration solutions in the treatment of cholera in children. Acta Paediatr 2000; 89: 787-790.
11. Maulen-Radovan I, Gutierrez-Castrellon P, Hashem M, Neylan M, Braggs G, Zaldo R, *et al*. Safety and efficacy of a premixed rice-based oral rehydration solution. J Pediatr Gastroenterol Nutr 2004; 38: 159-163.
12. Khin-Maung-U, Myo-Khin, Nyunt-Nyunt-Wai, Mu-Mu-Khin, Mya-Thi, Thein-Thein-Myint. Comparison of glucose / electrolyte and malto-dextrin / glycine / glycyl-glycine / electrolyte oral rehydration solutions in acute diarrhea in children. J Pediatr Gastroenterol Nutr 1991; 13: 397-401.
13. Grange A. Evaluation of malto-dextrin/glycine oral rehydration solution. Ann Trop Paediatr 1992; 12: 353-358.
14. Sabchareon A, Chongsuphajaisiddhi T, Kittikoon P, Chanthavanich P. Rice-powder salt solution in the treatment of acute diarrhea in young children. Southeast Asian J Trop Med Public Health 1992; 23: 427-432.
15. Murphy HH, Bari A, Molla AM, Zaidi A, Hirschhorn N. A field trial of wheat-based oral rehydration solution among Afghan refugee children. Acta Paediatr 1996; 85: 151-157.
16. Ibrahim S, Isani Z. Sagodana based verses rice based oral rehydration solution in the management of acute diarrhoea in Pakistani children. J Pak Med Assoc 1997; 47: 16-19.
17. Akosa UM, Ketiku AO, Omotade OO. The nutrient content and effectiveness of rice flour and maize flour based oral rehydration solutions. Afr J Med Med Sci 2000; 29: 145-149.
18. Alam NH, Meier R, Schneider H, Sarker SA, Bardhan PK, Mahalanabis D, *et al*. Partially hydrolyzed guar gum-supplemented oral rehydration solution in the treatment of acute diarrhea in children. J Pediatr Gastroenterol Nutr 2000; 31: 503-507.
19. Zaman K, Yunus M, Rahman A, Chowdhury HR, Sack DA. Efficacy of a packaged rice oral rehydration solution among children with cholera and cholera-like illness. Acta Paediatr 2001; 90: 505-510.
20. Hoekstra JH, Szajewska H, Zikri MA, Micetic-Turk D, Weizman Z, Papadopoulou A, *et al.* Oral rehydration solution containing a mixture of non-digestible carbohydrates in the treatment of acute diarrhea: a multicenter randomized placebo controlled study on behalf of the ESPGHAN working group on intestinal infections. J Pediatr Gastroenterol Nutr 2004; 39: 239-245.
21. Raghupathy P, Ramakrishna BS, Oommen SP, Ahmed MS, Priyaa G, Dziura J, *et al*. Amylase-resistant starch as adjunct to oral rehydration

therapy in children with diarrhea. J Pediatr Gastroenterol Nutr 2006; 42: 362-368.

22. Gutierrez C, Villa S, Mota FR, Calva JJ. Does an L-glutamine-containing, glucose-free, oral rehydration solution reduce stool output and time to rehydrate in children with acute diarrhoea? A double-blind randomized clinical trial. J Health Popul Nutr 2007; 25: 278-284.

23. Zavaleta N, Figueroa D, Rivera J, Sánchez J, Alfaro S, Lönnerdal B. Efficacy of rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme in Peruvian children with acute diarrhea. J Pediatr Gastroenterol Nutr 2007; 44: 258-264.

24. Alam NH, Ashraf H, Sarker SA, Olesen M, Troup J, Salam MA, *et al*. Efficacy of partially hydrolyzed guar gum-added oral rehydration solution in the treatment of severe cholera in adults. Digestion 2008; 78: 24-29.