Selected Summaries

Is starch the answer for cholera?

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SUMMARY

The absorptive capacity of the colon is considerably reduced in cholera. Ramakrishna *et al.* have evaluated the effects of non-absorbed amylase resistant starch added to standard glucose oral rehydration solution (ORS) on stool volume and diarrhoeal duration in patients with cholera. High amylose maize starch is resistant to digestion by amylases in the small intestine and passes unabsorbed into the colon when ingested uncooked. The hypothesis is that the short chain fatty acids produced by colonic fermentation of unabsorbed carbohydrates stimulate absorption of water and sodium in the colon. This is further supported by laboratory evidence that short chain fatty acid-linked sodium absorption is not inhibited by cyclic nucleotides and is upregulated by the action of cholera toxin.

Forty-eight adolescents and adults with diarrhoea for less than 72 hours and positive for *Vibrio cholerae* under dark field illumination were randomly assigned to receive treatment with one of the three ORSs; standard glucose ORS, standard glucose ORS with 50 g of uncooked rice flour per litre, or standard glucose ORS with 50 g of uncooked high amylose maize starch per litre. Randomization was done using permuted blocks of length six. The comparison groups were those receiving glucose-based ORS with or without rice flour. The solutions containing rice flour or high amylose starch were identical in appearance and the osmolarity of all the three solutions was 327 mOsm/L. Fluid therapy was given according to the World Health Organization (WHO) Plan B and a dose of 300 mg of doxycycline was given to all patients after 24 hours. All patients were encouraged to eat a standard south Indian vegetarian diet as soon as possible. The main outcome measures were stool weight measured after every 12 hours during the initial 48 hours following enrolment and diarrhoeal duration calculated as time taken from enrolment till the first formed stool. In addition, the transit time of faecal starch was measured in 6 patients who were given standard ORS with 50 g of high amylose maize starch.

The admission characteristics were comparable in the three groups. The stool weights were similar in the initial 36 hours for patients treated with standard glucose ORS with or without rice flour but was significantly less in the rice flour group during the 36–48-hour period (p=0.05). The group receiving ORS with resistant starch had significant reduction in stool weight as compared to those receiving standard glucose ORS in the 12–48 hours after enrolment, the difference being more marked in the 36–48-hour period. Similarly, the stool output was significantly reduced in the 36–48-hour period in the resistant starch group as compared to the rice flour group (p=0.01). The mean (SD) duration of diarrhoea in hours was significantly less in the group receiving ORS with resistant starch [56.7 (18.6)] as compared to the standard glucose ORS group [90.9 (29.8); p=0.001] and the rice flour ORS group [70.8 (20.2); p=0.01].

The authors concluded that addition of resistant starch to standard ORS significantly decreased stool output and diarrhoeal duration as compared to the standard ORS with or without rice flour in adolescents and adults with diarrhoea due to cholera.

COMMENT

For over two decades ORS recommended by the WHO has been used effectively and safely for all ages suffering from dehydration due to diarrhoea of cholera or non-cholera aetiology. However, it is well established now that it does not reduce stool output or shorten the duration of illness. This has prompted efforts to develop an ORS which could decrease the rate of fluid loss and shorten the duration of diarrhoea. The authors have evaluated the efficacy of one such solution.

In earlier evaluated ORSs the emphasis has been on improving the small bowel absorption of fluids by adding amino acids or by decreasing the osmolarity of the solution. Organic solutes are absorbed efficiently and relatively independently of each other, and enhance the absorption of sodium ions and water in the small intestine. Three actively absorbed amino acids—glycine (and glycyl–glycine), l-alanine and l-glutamine—were studied and patients with cholera were found to have a 30% less stool output than those given standard glucose ORS. These solutions are not recommended since they are more expensive and have no clinical advantage over the standard glucose ORS for children with acute non-cholera diarrhoea. In the second approach, glucose was replaced with rice in the standard ORS, thus increasing the amount of glucose available while decreasing the osmolarity of the solution. Studies with rice-based ORS using 50 g of cooked rice-powder per litre of solution have shown a 34% reduction in the initial stool output in children and adults with cholera diarrhoea. However, rice ORS and standard glucose ORS were found to be equally effective in children with non-cholera diarrhoea.[1] Low-osmolarity ORS with reduced concentrations of glucose and sodium have been evaluated, based on the hypothesis that the water absorption from such solutions is better than that from solutions isotonic with plasma. Low-osmolarity (224 mOsm/L) ORS has resulted in a 39% reduction in stool output and a 22% shorter duration of diarrhoea in non-cholera diarrhoea compared to standard ORS.[2] Adult cholera patients treated with low osmolarity ORS (245 mOsm/L) had a higher incidence of asymptomatic hyponatraemia but the solution was similar to standard ORS in terms of successful rehydration, diarrhoeal duration and stool output.[3]

Ramakrishna *et al.* evaluated a different approach; whether addition of amylase-resistant starch to standard glucose ORS would improve colonic absorption through production of short chain fatty acids during colonic fermentation of the unabsorbed starch. This study is important and relevant; however, the numbers evaluated are very small. It is difficult to understand why the authors have (i) used two comparison groups and (ii) added rice flour to the standard glucose ORS. In earlier trials, replacing glucose with rice reduced the osmolarity of the ORS. Also, there are no studies with rice flour added to standard glucose ORS. It also appears that the effect of the resistant starch ORS on the initial 24-hour stool output is much less than that of the rice-based ORS. The earlier meta-analysis reported a mean reduction of 34% (95% CI: 25%–43%) of the initial 24-hour stool output with rice-based

ORS as compared to the standard glucose ORS in children and adults with cholera diarrhoea.[1] In the present study the initial 24-hour stool output was only 14% less in the resistant starch ORS group as compared to the standard glucose ORS group. This may well be because all the patients in this study were started on a rice-based diet promptly after rehydration in contrast to the earlier studies with rice-based ORS where early feeding was not routinely recommended.

Routine administration of antimicrobials at the beginning of the illness has been found to decrease the duration of illness to less than 48 hours and reduce stool output during the latter part of the illness. The benefits of the resistant starch solution during the later period may not have been so marked if antimicrobials had been administered at the time of enrolment and not after 24 hours. However, the study size was not adequate to give a precise estimate of the differences.

The use of short chain fatty acids to stimulate absorption of water and electrolytes in the colon during diarrhoea is important and needs to be evaluated further in a larger number of subjects.

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Efficacy of monovalent human rotavirus vaccine 89-12 in infants

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SUMMARY

Rotavirus is a major cause of acute gastroenteritis and the commonest cause of severe dehydrating diarrhoea in infants all over the world. This randomized, placebo-controlled, double-blind multicentric trial aimed to assess the safety, immunogenicity and efficacy of a live oral monovalent vaccine 89-12.[1] 89-12 is an attenuated G1 (P8) human isolate originally obtained from a rotavirus-infected infant in Cincinnati, USA. The basis for selecting this isolate was that many reports have documented the protective effects of natural infections with rotavirus subtype 89-12 against subsequent rotavirus disease and so vaccines that more closely mimic human infection would provide greater protection.

This study included 215 healthy infants between 10 and 16 weeks of age; 213 of them received an oral dose of 1 ml of vaccine (1×10^{-5} pfu) or placebo. Two such doses of vaccine or placebo were given at an interval of 6–10 weeks. They were then followed up for one rotavirus season. Immune response to rotavirus was assessed by serum and stool IgA and serum 89-12 neutralizing antibodies. The primary outcome variable (protection from rotavirus disease) was evaluated by comparing the frequencies of rotavirus gastroenteritis in an intention-to-treat analysis.

Immune response was detected in 94.4% of vaccinees. Rotavirus disease occurred in 18 of 107 placebo recipients and 2 of 108 vaccine recipients (vaccine efficacy 89%, 95% CI 65.4%–94.6%). Ten infants in the placebo group but none in the vaccine group presented for medical care. Adverse reactions were minimal, occurring only in the form of mild fever in the vaccine group (in 19% of the vaccine group and 5% of the placebo group).

COMMENT

The 89-12 rotavirus vaccine was found to be safe and immunogenic and provided a high degree of protection against rotavirus disease. The 89-12 vaccine contains only one strain and the protection offered is quite high (89%) as compared to the tetravalent rhesus rotavirus reassortant vaccine whose protection ranged from 49% in the largest American study to 68% in a Finnish study.[1,2] The immunogenicity of the vaccine was also high; 94.4% of vaccine recipients responded to vaccination as shown by serum rotavirus-specific IgA (91.4%) or neutralizing antibody (69.2%) to the G1 rotavirus strain 89-12. The immunogenicity of the tetravalent reassortant vaccine was also found to be similar in previous studies (approximately 90%)[2,3] but only 28%–31% of participants in those studies developed neutralizing antibodies to any of the four most common human serotypes G1–G4 (the most commonly circulating serotypes). The major immune response was to rhesus rotavirus. However, the correlation between serum neutralizing antibody levels and clinical protection is yet to be established and so the differences in the immune responses should be interpreted with caution.

The vaccine appears safe. Like the tetravalent vaccine, it causes mild fever (19.4%), with an incidence similar to that in the American and Finnish studies. Other side-effects are comparable to the placebo group. A potential concern is that the live vaccine virus may revert to a virulent form during replication in infected infants. Studies of nucleotide sequences are being done to compare the gene sequences in the vaccine preparation with those of unpassaged 89-12 virus and 89-12 isolates shed by vaccinated infants.

The authors concluded that the use of an attenuated human strain rather than animal rotaviruses may offer better protection because it is more closely related to human strains. Also, the use of only one strain and two doses may reduce the cost.

In India, rotavirus is detected in 5%–15% of infants with mild diarrhoea, and in 20%–40% of children with severe diarrhoea. The G serotype 9 is an important cause which is not included in the tetravalent vaccine.[3] Limited studies in developing countries sug-