Impact of glycine-containing ORS solutions on stool output and duration of diarrhoea: a meta-analysis of seven clinical trials

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The results are described of a meta-analysis of seven randomized trials that compared the clinical effects of the standard solution of WHO oral rehydration salts (ORS), containing 20 g/l of glucose, and experimental ORS solutions, containing glycine, on 643 children with acute noncholera diarrhoea. The availability of data on individual patients in each trial permitted the scope of the meta-analysis to be enhanced because the data could be pooled after adjusting for differences in baseline patient characteristics; also, the statistical strategy in terms of data quality, post-randomization exclusion of patients, and regression modelling could be standardized for all trials. The results of the analysis showed that neither stool output nor duration of diarrhoea was reduced by the experimental formulations. Only for weight gain was there a statistically significant difference between the treatment groups (those given the WHO–ORS solution gained less weight). This probably reflects transient excess fluid retention within the gut lumen or tissues of the patients who received the glycine-containing solutions. ORS formulations that contain glycine are therefore not clinically superior to the WHO–ORS solution.

Introduction

The current formulation of oral rehydration salts (ORS) recommended by WHO and UNICEF is effective for treating patients of all ages who have dehydration caused by acute diarrhoea of any etiology.[a] The formulation has, however, no effect on the volume, frequency, and duration of diarrhoea (*1–4*), which raises problems of user acceptance and satisfaction, since a major concern of mothers (and also of health care providers) is the frequency of children's stools and the duration of diarrhoeal episodes.

The physiological basis for the effectiveness of ORS solution is the coupled active transport of sodium and glucose across the brush border membrane of the enterocyte (*5*), which results in passive absorption of water and electrolytes. Other water-soluble organic molecules, such as glycine, also stimulate sodium absorption from the gut independently from glucose (*6, 7*). Addition of glycine to the current WHO–ORS formulation might therefore increase absorption of sodium from the small intestine. This might lead to the development of an ORS formulation that would not only be absorbed, but which would induce reabsorption of intestinal secretions and thus reduce the volume and duration of diarrhoea, i.e., it would act as an absorption-promoting antidiarrhoeal drug.[b]

Such a possibility was suggested by the results of two clinical trials, one on adults and the other on children with acute diarrhoea, which showed that the addition of glycine (110 mmol/l) to the WHO–ORS solution caused a significant reduction in stool volume and duration of diarrhoea (*8, 9*). However, most patients in these studies had toxigenic diarrhoea caused either by *Vibrio cholerae* or by enterotoxigenic *Escherichia coli* (ETEC). In two other clinical trials of children with acute diarrhoea caused mainly by rotavirus, no therapeutic advantage was observed for the glycine/glucose–ORS solution compared with the WHO–ORS (*10, 11*). The lack of an enhanced benefit for the glycine-containing solution in cases of rotavirus diarrhoea may reflect its distinct hypertonicity (theoretical osmolarity = 430 mmol/l versus 330 mmol/l for the WHO–ORS solution): a hypertonic fluid would increase stool volume if the

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[a] *A manual for the treatment of diarrhoea*. Unpublished document WHO/CDD/SER/80.2 Rev.2.

[b] **Mahalanabis, D.** *Development of an improved formulation of oral rehydration salts (ORS) with anti-diarrhoeal and nutritional properties: a "super ORS"*. WHO unpublished document CDD/DDM/85.3.

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absorption of glucose or glycine was incomplete owing to rotavirus-induced mucosal damage to the proximal small intestine.

These considerations led the WHO Diarrhoeal Disease Control Programme to support several studies to evaluate further the relative efficacy of glycine-containing ORS solutions in children with acute diarrhoea caused by various agents, including both bacteria and rotavirus. Six glycine-containing ORS formulations of different osmolarities were tested in nine clinical trials. The following approaches were used to keep the osmolarity of these ORS solutions as close as possible to that of the WHO–ORS solution, without modifying the electrolyte level: reducing the glucose content of the solution; providing part of the amino acid as a dipeptide (glycylglycine); and replacing the glucose by maltodextrins (glucose polymers).

We report here a meta-analysis of the above-mentioned studies that sought to determine whether the experimental ORS formulations were more effective than the WHO–ORS solution.

Standard record forms developed by a clinician (*D.M.*) and a statistician (*S.M.G.*) were used in seven of the studies; two additional studies that were carried out before these forms were developed (in Myanmar and Peru) are not included in the analysis. The use of standard record forms enabled a large database to be set up and expanded the repertoire of statistical analyses employed, to include extensive data checking; multifactorial regression methods to investigate prognostic factors for stool volume and ORS solution intake; and a meta-analysis that compared the efficacy of WHO–ORS solution and other formulations. The scope of the meta-analysis was enhanced by the availability of data on individual patients in each trial because pooling could be performed after adjusting for the influence of differences in baseline patient characteristics; and the statistical strategy for data quality, post-randomization exclusion of patients, and regression modelling could be standardized for all trials.

Subjects and methods

Characteristics of the clinical trials

Of the seven studies listed in Table 1, six were initiated in 1986 and used standard record forms; the seventh, which began in 1985, provided conformable data. One study (No. 3) compared two glycine-based ORS formulations with the WHO–ORS solution; the results obtained have been combined in regressions and in the meta-analysis.

Some patients were excluded from all the analyses or from those that required data after the first 24 hours of the study, either because the investigators failed to monitor them after detecting clinical problems or because the patients were discovered to have been ineligible. Exclusions were made for any of the following reasons: persistent diarrhoea on entry; mild dehydration and no diarrhoea; pneumonia or meningitis on admission; withdrawal of parental consent within 24 hours; unblinding of the study because of a change in the physical appearance of the study ORS with time; or failure to monitor the child after giving unscheduled intravenous fluids. Children whose parents removed them from the

Table 1: **Characteristics of the seven clinical trials analysed in the study**

Study No.	Location	Composition of experimental ORS formulation	Osmolarity of ORS (mmol/l)	Age of subjects (years)	No. of subjects randomized at 24 hours	No. of subjects followed to the end
1	Philippines	Glucose, 20 g; glycine, 4 g; glycylglycine, 4 g	387	<3	66 (65)[a]	66, *65*[b]
2	India	Maltodextrin MD25, 20 g; glycine, 4 g; glycylglycine 4 g	326	<2	93 (90)	92, *88*
3	Egypt	Maltodextrin MD25, 20 g; glycine, 4 g; glycylglycine 4 g	326	<3	150 (150)	150, *150*
		Maltodextrin MD25, 20 g; glycine, 8 g	356	<3	150 (150)	150, *150*
4	India	Maltodextrin MD25, 20 g; glycine, 4 g; glycylglycine, 4 g	326	<5	33 (32)	33, *32*
5	Venezuela	Maltodextrin MD25, 20 g; glycine, 4 g; glycylglycine, 4 g	326	<3	150 (147)	148, *143*
6	Costa Rica	Glucose, 12 g; glycine, 4 g; glycylglycine, 4 g	342	<2	62 (62)	62, *62*
7	Nigeria	Maltodextrin MD25, 20 g; glycine, 8 g	356	<3	89 (59)	89, *59*

[a] Figures in parentheses are the number of subjects for whom data were analysed for the first 24 hours.
[b] Figures in italics are the number of subjects for whom data were analysed up to the end of the study.

study after 48 hours were classified as having terminated diarrhoea at the time of their discharge, and the total stool weight was that recorded during their stay as inpatients. This procedure accords with the parents' view that their children had recovered.

The number of subjects in the studies ranged from 32 to 150 infants and children. The mean theoretical osmolarity of the experimental solutions was 343 mmol/l (range, 326–387 mmol/l), while the theoretical osmolarity for the WHO–ORS solution was 330 mmol/l. Only one study (No. 4) admitted children up to the age of 5 years; otherwise the upper age limit was 2 or 3 years.

Statistical strategy

Initially, each trial was checked for baseline characteristics and measured outcomes (unadjusted for covariates) of children who were given the WHO–ORS solution. The summarized data were carefully validated and outlying values were identified by inspecting frequency tables and conducting two-way analyses, e.g., by plotting stool output against ORS solution intake in the first 24 hours, or by plotting the logarithm of the child's weight against the logarithm of age on admission.

Next, a multifactorial analysis of the results of the individual trials was carried out to identify covariates that influenced specific outcomes and to determine whether the influences were homogeneous between trials. This allowed us to adjust the outcome variables for the influence of differences in baseline patient characteristics. Two sorts of adjustment were made. In the first, we assumed that the influence of covariates that influenced specific outcomes and to made common adjustments for a global set of covariates. In the second, the set of covariates for which adjustments should be made was determined, but the nature of the adjustments was optimized for each trial. The following simple covariate set was explored: disease characteristics (duration of diarrhoea before admission, skin elasticity on admission); biochemical data (serum sodium concentration on admission or haematocrit on admission); and patient characteristics (weight or age on admission, or the ratio of the logarithm of admission weight to the expected logarithm of admission weight for age).

The third phase of the statistical strategy was to combine inferences about the WHO–ORS solution versus experimental formulations from the individual trials in a meta-analysis, which was performed first without adjusting for covariates and weighted in inverse proportion to the variance of the between-formulation differences in the means (S. M. Gore et al., unpublished results, 1991). The meta-analysis was then performed after adjusting for a global set of covariates, again weighted in inverse proportion to the variance of the between-formulation differences in the mean outcome variables.

Results

Patient characteristics

The baseline characteristics of the children in the seven studies are summarized in Table 2. Except for study No. 4, the mean values were similar in all the studies; in study No. 4, however, the mean age was higher, the mean duration of illness before admission shorter, the mean haematocrit higher, and the mean serum sodium concentration lower. These differences probably reflect the higher proportion of children with cholera in this study. In all studies, 70% or more of patients had sunken eyes on admission. The modal skin elasticity ranged from normal to moderately diminished and, except for one study, the modal score for skin elasticity was the same as the mode for dehydration, evaluated clinically (data not shown).

Outcome variables

For children treated with WHO–ORS solution, the means and standard deviations for selected outcome variables from individual studies are summarized in Table 3. The standard deviation of stool output in the first 24 hours varied widely, and was greatest

Table 2: **Patient characteristics on admission to the studies**

Study No.	Mean age ± SD (months)	Mean admission weight ± SD (kg)	Mean duration ± SD of illness before admission (hours)	Mean haematocrit ± SD on admission (%)	Mean serum sodium level ± SD on admission (mmol/l)
1	12 ± 7	7.1 ± 1.6	57 ± 37	35 ± 4	132 ± 7
2	9 ± 6	6.5 ± 1.5	46 ± 25	36 ± 6	134 ± 9
3	11 ± 5	8.0 ± 1.7	47 ± 22	35 ± 4	133 ± 10
4	25 ± 19	8.2 ± 2.7	19 ± 13	41 ± 6	125 ± 7
5	10 ± 6	8.2 ± 2.0	45 ± 29	38 ± 4	140 ± 10
6	8 ± 5	6.9 ± 1.9	63 ± 24	38 ± 5	139 ± 8
7	10 ± 6	8.1 ± 1.3	46 ± 30	36 ± 4	135 ± 6

Table 3: **Outcome variables for children given the WHO–ORS solution**

Study No.	0–24 hours: Mean stool output ± SD (g)	0–24 hours: Mean ln (ORS intake in ml) ± SD	0–24 hours: Mean ln (stool output in g) ± SD	0 to end of study: Mean ln (stool output in $g.kg^{-1}.24\ h^{-1}$) ± SD	Mean ln (duration of illness in h) ± SD	% mean weight gain ± SD on discharge
1	1114 ± 1570	6.2 ± 0.6	6.5 ± 1.0	4.6 ± 0.9	3.6 ± 0.7	5.3 ± 4.2
2	730 ± 547	7.0 ± 0.4	6.4 ± 0.7	4.8 ± 0.6	3.8 ± 0.5	2.5 ± 4.6
3	680 ± 396	7.3 ± 0.5	6.4 ± 0.6	4.6 ± 0.6	3.8 ± 0.6	3.6 ± 2.8
4	1019 ± 925	7.5 ± 0.7	6.5 ± 1.1	4.7 ± 0.7	3.4 ± 0.8	6.4 ± 5.0
5	863 ± 547	7.3 ± 0.4	6.5 ± 0.8	4.5 ± 0.7	3.6 ± 0.6	3.7 ± 4.3
6	769 ± 524	7.4 ± 0.3	6.4 ± 0.7	4.6 ± 0.5	4.0 ± 0.6	5.8 ± 4.3
7	539 ± 288	6.6 ± 0.3	6.2 ± 0.5	4.7 ± 0.6	2.9 ± 0.6	4.3 ± 3.9
Pooled SD	—	0.4	0.8	0.7	0.6	4.2

when the mean stool output was high and least when it was low. After logarithmic transformation, the between-trial variance of the outcome variables still exhibited some heterogeneity, but the ratio of maximum to minimum variance diminished, e.g., from about 30 to 4 for the logarithm ($\ln = \log_e$) of stool output in the first 24 hours. Table 3 also shows the pooled standard deviations for ln (ORS solution intake) and ln (stool output). The lower standard deviation for the former (0.4) than for the latter (0.8) suggests that differences in the performance of the ORS formulations would more readily be detected by comparing the average ln (ORS solution intake) rather than the average ln (stool output) for the different treatment groups.

Apart from study No. 1, the averages for ln (stool output), ln (stool output per kg per 24 hours), and ln (ORS solution intake in the first 24 hours) were remarkably homogeneous between studies. Table 3 also shows the homogeneity of variance between trials for the ln (duration of illness). Between-trials heterogeneity occurs for this outcome, since the duration was appreciably shorter in study No. 7 than in the others. In addition, the average weight gain in study No. 2 was appreciably lower than that in studies No. 4 and No. 6.

Meta-analysis

Unadjusted for covariates. Before considering regression models, we reviewed the summary comparisons, unadjusted for covariates, of the average differences in outcomes for WHO–ORS solution versus other ORS formulations in the seven individual studies (Table 4). Also shown in Table 4 are the weights assigned to each outcome variable in each study, which were used to calculate the pooled mean differences, the pooled standard errors of the mean differences (Table 4), and the 95% confidence intervals of the pooled mean differences shown in Table 7.

Table 4 indicates that only two studies had mean differences in the intake of ORS solution in the first 24 hours that were significant at the 10% level. The negative differences in four trials indicate greater intake of ORS solution (and also in stool output) for patients given the experimental formula.

Table 4 also shows the average differences in ln (stool output per kilogram per 24 hours of diarrhoea) and in ln (duration of diarrhoea). For the latter outcome, only one study reported a mean difference that was significant at the 10% level. There was little agreement among studies in terms of the sign of the mean difference between formulations for either outcome.

Two studies reported a significantly greater weight gain with the WHO–ORS solution than with the experimental formulation ($P < 0.1$); however, all the other studies reported that the average weight gain associated with the WHO–ORS solution was less than that with the experimental solutions.

Multiple regression: pooled data. The above-mentioned findings for unadjusted covariates suggest that the regression coefficients for the comparison between the WHO–ORS solution and the experimental formulations should be close to zero for all outcome variables and not statistically significant, with the possible exception of weight gain.

Regression coefficients (and *P*-values) are shown in Table 5 for the covariates that describe disease characteristics and laboratory data.

The regression coefficients in Table 5 indicate that the covariates which influence ln (stool output) and ln (ORS solution intake in the first 24 hours) are duration of diarrhoea in days before admission (the longer the pre-admission duration of diarrhoea, the lower the ln (stool output) and ln (ORS solution intake) in the first 24 hours); and skin elasticity (highly significantly greater stool output was associated with greater loss of skin elasticity). These

Table 4: **Unadjusted outcome variables for WHO–ORS solution minus those for the experimental ORS solutions**

Study No.	0–24 hours: ln (ORS intake in ml) Mean difference	Variance	0–24 hours: ln (stool output in g) Mean difference	Variance	0 to end of study: ln (stool output in $g.kg^{-1}.24\ h^{-1}$) Mean difference	Variance	ln (duration of illness in hours) Mean difference	Variance	% weight gain Mean difference	Variance
1	−0.16[a]	0.022 (0.06)[b]	−0.36	0.060 (0.06)	−0.33	0.040 (0.07)	−0.26	0.026 (0.10)	−1.98	1.48 (0.08)
2	0.03	0.008 (0.17)	0.17	0.022 (0.16)	−0.14	0.018 (0.15)	0.21	0.017 (0.16)	−2.06	0.82 (0.14)
3	−0.10	0.006 (0.20)	−0.78	0.011 (0.33)	−0.01	0.010 (0.28)	−0.01	0.011 (0.23)	−1.21	0.35 (0.33)
4	0.01	0.051 (0.02)	0.72	0.316 (0.01)	0.64	0.157 (0.02)	0.15	0.102 (0.02)	−0.10	5.04 (0.02)
5	−0.14[a]	0.005 (0.27)	−0.28	0.017 (0.21)	−0.18[a]	0.011 (0.25)	−0.16[a]	0.008 (0.31)	0.19[a]	0.53 (0.21)
6	−0.14	0.009 (0.14)	−0.14	0.038 (0.10)	0.05	0.022 (0.12)	0.13	0.023 (0.11)	−1.28	1.03 (0.11)
7	0.15	0.009 (0.14)	0.20	0.029 (0.12)	0.25	0.024 (0.12)	−0.05	0.040 (0.07)	1.42[a]	1.12 (0.10)
Pooled mean difference	−0.06		−0.06		−0.04		−0.03		−0.80	
Pooled standard error	0.04		0.06		0.05		0.05		0.34	

[a] $P < 0.1$.
[b] Figures in parentheses are the weights assigned to each outcome variable.

covariates exert similar, but much reduced, influences on the ln (total stool output), with only skin elasticity retaining formal statistical significance.

For ln (duration of diarrhoea), all four covariates in Table 5 were predictive: reduced skin elasticity and a higher haematocrit on admission are indicative of a longer duration of diarrhoea; and a longer pre-admission duration of diarrhoea and higher serum sodium level on admission indicate a shorter duration of diarrhoea after admission, as does older age on admission. Finally, lower skin elasticity, higher haematocrit, and a higher serum sodium level on admission each predict a greater percentage weight gain.

By trial adjustment. The same outcome variables as in Table 4 are shown in Table 6, after trial-specific adjustment for the above-mentioned covariates.

Table 5: **Multiple regression coefficients for the pooled outcome data**

Covariate	0–24 hours: ln (ORS intake in ml) Coefficient	*P*-value	0–24 hours: ln (stool output in g) Coefficient	*P*-value	0 to end of study: ln (stool output in $g.kg^{-1}.24\ h^{-1}$) Coefficient	*P*-value	ln (duration of illness in hours) Coefficient	*P*-value	% weight gain Coefficient	*P*-value
Disease characteristics										
Duration before admission	−0.04	0.01	−0.08	0.01	−0.04	0.12	−0.07	0.004	−0.01	0.96
Skin elasticity	0.24	<0.001	0.32	<0.001	0.15	0.01	0.19	0.002	1.14	0.01
Laboratory data										
Haematocrit on admission	0.004	0.29	0.014	0.06	0.006	0.34	0.016	0.01	0.04	0.001
Sodium level on admission	zero	0.95	zero	0.94	zero	0.89	−0.01	0.02	0.07	0.001

Table 6: **Adjusted outcome variables (WHO–ORS solution minus the experimental ORS solutions)**

Study No.	0–24 hours: ln (ORS intake in ml) Mean difference	Variance	0–24 hours: ln (stool output in g) Mean difference	Variance	0 to end of study: ln (stool output in g.kg^{-1}.24 h^{-1}) Mean difference	Variance	ln (duration of illness in hours) Mean difference	Variance	% weight gain Mean difference	Variance
1	−0.06	0.025 (0.05)[a]	−0.11	0.066 (0.06)	−0.05	0.038 (0.07)	−0.12	0.024 (0.11)	−1.17	1.22 (0.10)
2	0.05	0.007 (0.16)	0.21	0.025 (0.15)	−0.14	0.016 (0.15)	0.27	0.018 (0.15)	−2.19	0.86 (0.15)
3	−0.09	0.007 (0.18)	−0.07	0.012 (0.31)	0.02	0.009 (0.29)	0.01	0.012 (0.22)	−0.98	0.47 (0.27)
4	0.26	0.069 (0.02)	1.38	0.470 (0.01)	0.92	0.273 (0.01)	0.62	0.080 (0.03)	−1.74	2.58 (0.05)
5	−0.14	0.004 (0.29)	−0.25	0.014 (0.27)	−0.16	0.009 (0.30)	−0.29	0.008 (0.38)	−0.10	0.54 (0.24)
6	−0.07	0.008 (0.16)	−0.17	0.039 (0.10)	−0.06	0.028 (0.09)	−0.01	0.023 (0.12)	−1.37	1.26 (0.10)
7	−0.12	0.009 (0.14)	0.20	0.036 (0.11)	0.26	0.029 (0.09)	0.04	0.054 (0.05)	−0.08	1.36 (0.09)
Pooled mean difference	−0.04		−0.05		−0.04		−0.02		−0.96	
Pooled standard error	0.03		0.06		0.05		0.05		0.36	

[a] Figures in parentheses are the weights assigned to each outcome variable.

Table 6 also indicates the relative weights that were assigned to each study for each outcome variable, after adjustment, which were used to calculate the pooled mean difference, its standard error, and the 95% confidence intervals shown in Table 7.

Summary. Table 7 shows the 95% confidence intervals for the major outcome variables, determined as follows: by meta-analysis, unadjusted for covariates, and weighted inversely to the variance of between-formulation differences in means for individual trials; by regression analysis, after common adjustment for baseline characteristics; and by meta-analysis, after specific trial adjustment for baseline characteristics and weighting inversely to the variance of the adjusted between-formulation differences in the means from individual trials.

Only for weight gain did the 95% confidence interval lie entirely to one side of zero, which indicates a statistically significant difference between patients treated with WHO–ORS solution and the glycine-containing formulations (children who received the WHO–ORS solution gained less weight). The results of the meta-analysis clearly demonstrated that neither stool output nor duration of diarrhoea was reduced by the experimental formulations. Finally, with the exception of weight gain, the confidence intervals were not altered markedly by adjustment for covariates. This suggests that the covariate imbalances between patients assigned at random to

Table 7: **95% confidence intervals for the major outcome variables for the WHO–ORS solution minus other ORS formulations**

Method	0–24 hours: ln (ORS intake in ml)	0–24 hours: ln (stool output in g.kg^{-1}.24 h^{-1})	0 to end of study: ln (stool output in g.kg^{-1}.24 h^{-1})	ln (duration of illness in hours)	% weight gain
Meta-analysis (unadjusted)	−0.13 to 0.01	−0.18 to 0.06	−0.14 to 0.06	−0.13 to 0.07	−1.46 to −0.1
Regression analysis (common adjustment)	−0.13 to 0.01	−0.18 to 0.10	−0.13 to 0.07	−0.11 to 0.09	−1.50 to −0.1
Meta-analysis (by trial adjustment)	−0.11 to 0.03	−0.17 to 0.07	−0.14 to 0.06	−0.12 to 0.08	−1.66 to −0.2

WHO–ORS solution and other formulations were not important.

Discussion

The results of individual studies to evaluate the effect of glycine-containing ORS formulations on stool output and duration of diarrhoea are conflicting. For such solutions several studies have reported statistically significant reductions in the volume of stool output and duration of diarrhoea, or in the consumption of ORS solution. These studies involved both adults with cholera (*8*) (A. Moechtar, personal communication, 1988) and children with acute non-cholera diarrhoea (*9*, *13*, *14*). However, other studies failed to demonstrate any advantage for ORS solutions containing glycine (*10*, *11*, *12*, *15*). The results of the present meta-analysis of seven randomized double-blind trials clarify this ambiguity: ORS formulations containing glucose (or maltodextrin) and glycine (or glycylglycine) are not clinically superior to the standard WHO–ORS solution. The confidence intervals for the comparisons of ORS solutions exclude any clinically worthwhile reduction in the volume of stool output or duration of diarrhoea in patients who received the experimental solutions. The results from two WHO-supported studies that were not included in the present analysis (Khin Maung U & E. Salazar-Lindo, personal communication, 1988) are consistent also with this conclusion. To explain the lack of any clinical advantage for ORS solutions containing glycine, we assume that glucose and glycine are approximately equally effective in enhancing sodium absorption from the bowel lumen and that all the glucose in an isotonic ORS solution contributes to sodium absorption. Thus, the potential beneficial effect of adding glycine to an isotonic ORS solution is negated by the hypertonicity that results. If, however, the concentration of glucose is lowered enough to ensure that the glycine-containing ORS solution is isotonic, the glycine-containing formulation still offers no net advantage.

The pooled analysis of the results of the seven studies indicated that weight gain after initial rehydration was 10% greater with the experimental ORS formulations than with WHO–ORS solution; however, increased weight is not necessarily a clinical benefit. Since all the patients were judged to be fully rehydrated when their post-rehydration weight was determined, the greater weight gain (associated with greater intake of ORS solution) may reflect transient excess fluid retention within the gut lumen or tissues—the mechanism of such an effect is nevertheless not clear. The greater weight gain was not due to a difference in food intake, since all weights were determined before feeding was resumed.

The above analysis demonstrates the importance of logarithmic transformation in reducing the heterogeneity of variance between trials of ORS solutions. The variable that was transformed to the greatest extent (the logarithm of stool output per kilogram of admission weight per 24 hours for the entire diarrhoeal episode) was also the outcome measure that yielded the most similar results for the between-trial means for the WHO–ORS solution.

Finally, multifactorial analysis revealed few instances of outlying results. Overall, the retrospective adjustments for covariate imbalances between groups were small, as would be expected in well-randomized trials.

Résumé

Effet des solutions de SRO contenant de la glycine sur le volume des selles et la durée de la diarrhée: méta-analyse de sept essais cliniques

La formulation des sels de réhydratation orale (SRO) recommandée par l'OMS et l'UNICEF permet de traiter la déshydratation par diarrhée aiguë (quelle qu'en soit l'étiologie) chez les malades de tous âges; toutefois, elle n'a aucun effet sur le volume, la fréquence et la durée de la diarrhée. On a rapporté que l'adjonction de glycine (un acide aminé qui stimule l'absorption du sodium à partir de l'intestin indépendamment du glucose) à une solution de SRO-OMS dans deux essais cliniques portant l'un sur des adultes et l'autre sur des enfants atteints de diarrhée aiguë, avait provoqué une diminution statistiquement significative du volume des selles et de la durée de la diarrhée. Cependant, deux autres essais cliniques portant sur des enfants atteints de diarrhée aiguë n'ont pas démontré que la solution de SRO avec glycine présentait un quelconque avantage thérapeutique sur la solution OMS classique. Le Programme OMS de Lutte contre les Maladies diarrhéiques a donc été conduit à soutenir plusieurs études afin de mieux évaluer l'efficacité relative des solutions de SRO avec glycine chez les enfants atteints de diarrhée aiguë provoquée par divers germes, notamment des bactéries et des rotavirus.

On a testé six formulations de SRO avec glycine de différentes osmolalités. Nous rapportons ici une méta-analyse de ces études, qui visaient à déterminer si les formulations expérimentales ont été plus efficaces que la solution de SRO classique de l'OMS: les études ont porté sur 643 enfants atteints de diarrhée aiguë non cholé-

rique. La possibilité de disposer de données concernant chaque malade dans chaque essai a permis de renforcer la portée de cette méta-analyse, car on a pu regrouper les données après les avoir corrigées des caractéristiques individuelles de chaque malade; en outre, on a pu normaliser dans tous les essais la stratégie statistique en ce qui concerne la qualité des données, l'exclusion des malades après randomisation, et les modèles de régression.

Les intervalles de confiance à 95% pour les principales variables intéressantes ont été déterminés de la manière suivante: par méta-analyse, sans correction des covariables et après pondération en proportion inverse de la variance des différences entre formulations observées dans les moyennes de chaque essai; par analyse de régression, après correction générale des caractéristiques individuelles; et par méta-analyse, après correction pour chaque essai des caractéristiques individuelles et pondération en proportion inverse de la variance des différences entre formulations observées dans les moyennes de chaque essai. Les résultats montrent qu'il n'y a de différence statistiquement significative qu'au niveau du gain de poids entre les différents groupes de traitement (ceux ayant reçu la solution de SRO-OMS classique ayant moins gagné de poids). Cela s'explique probablement par une rétention transitoire des liquides en excès dans la lumière intestinale ou les tissus des malades ayant reçu des solutions contenant de la glycine. La méta-analyse montre clairement que ni le volume des selles, ni la durée de la diarrhée n'ont été diminués avec ces formulations expérimentales. Nous concluons donc que les formulations de SRO avec glycine ne présentent aucun avantage clinique sur les solutions de SRO-OMS.

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