Rice-based oral rehydration solution for treating diarrhoea
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A substantive amendment to this systematic review was last made on 02 August 1998. Cochrane reviews are regularly checked and updated if necessary.

Background: Oral rehydration therapy is used to treat dehydration caused by diarrhoea. However the rehydration solution does not reduce stool loss or length of illness. A solution able to do this may lessen the use of ineffective diarrhoea treatments as well as improve morbidity and mortality related to diarrhoea.

Objectives: The objective of this review was to assess the effects of rice-based oral rehydration salts solution compared with glucose-based oral rehydration salts solution on reduction of stool output and duration of diarrhoea in patients with acute watery diarrhoea.

Search strategy: We searched the Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, Medline, Embase, Lilacs and the reference lists of relevant articles. We also contacted researchers in the field.

Selection criteria: Randomized trials comparing standard World Health Organization oral rehydration solution with an experimental oral rehydration salts solution in which glucose (20 grams per litre) was replaced by 50-80 grams per litre of rice powder, with the electrolytes remaining unchanged.

Data collection and analysis: Data were extracted independently by a statistician and a clinician.

Main results: Twenty-two trials were included. Concealment of allocation was adequate in 15 of these trials. Irrespective of age, people with cholera who were given rice oral rehydration salts solution had substantially lower rates of stool loss than those given oral rehydration salts solution in the first 24 hours. Mean stool outputs in the first 24 hours were lower by 67 millilitres/kg of body weight (weighted mean difference -67.4, 95% confidence interval -94.3 to -41.0) in children, and by 51 millilitres/kg of body weight (weighted mean difference -51.1, 95% confidence interval -65.9 to -36.3) in adults. The rate of stool loss in infants and children with acute non-cholera diarrhoea was reduced by only four millilitres/kg of body weight (weighted mean difference -4.3, 95% confidence interval -9.3 to 0.8).

Reviewers’ conclusions: Rice-based oral rehydration appears to be effective in reducing stool output in people with cholera. This effect was not apparent in infants and children with non-cholera diarrhoea.

Background
Oral rehydration therapy with glucose and electrolyte solution recommended by the World Health Organization and Unicef is used to treat children with dehydration caused by diarrhoea, provided they are able to drink and do not have signs of shock (1). Although the solution is both safe and effective (D. Mahalanabis, unpublished document), it has important limitations: it neither reduces the rate of stool loss nor shortens the duration of illness (2-5). Mothers often do not understand the relation between diarrhoea and dehydration, and their primary concern, shared by many health workers, is to see the diarrhoea stop. This probably accounts for the continuing widespread use of ineffective “anti-diarrhoeal” drugs and antibiotics to treat diarrhoea instead of, or in addition

If a packaged oral rehydration salts formulation could be developed that not only had the positive features of WHO formulation, including low cost and safety and stability during prolonged storage, but also substantially reduced the duration of diarrhoea or the rate of stool loss, it would have considerable advantages. In particular, it could be promoted as having real antidiarrhoeal effect. This should improve its acceptance and use by both health workers and mothers, especially if its benefits were sufficiently great to be evident to them. It might also result in less use of ineffective drugs and antibiotics. Such changes would represent a major advance in efforts to control morbidity and mortality associated with diarrhoea through effective case management.

Several clinical trials have shown that an oral rehydration salts solution containing cooked rice powder (50-80g/l) in place of the usual glucose (20g/l) substantially reduces the rate of stool loss due to acute diarrhoea (6-10). Other studies, however, have reported no significant benefit (11-14). The patients in these studies varied considerably and included infants, children, and adults both with diarrhoea associated with cholera and with acute diarrhoea not associated with cholera. Moreover, in some studies the number of patients evaluated was probably insufficient to support firm conclusions. To define more precisely the true benefit of rice oral rehydration salts solution in relation to the WHO oral rehydration salts solution and to determine whether this benefit is related to the patient’s age or the aetiology of diarrhoea we performed a systematic review using data from all available randomized clinical trials that compared these two formulations.

**Objectives**

To compare rice oral rehydration salts solution (containing 50-80 g/l of rice powder) with glucose oral rehydration salts solution (WHO standard).

Explore the hypotheses:

- Benefit is related to the patient’s age
- Benefit is related to whether or not the diarrhoea is caused by cholera

**Criteria for considering studies for this review**

**Types of studies**

Randomized trials. Trials with alternate allocation were excluded.

**Types of participants**

Children or adults with signs of dehydration due to acute diarrhoea.

**Types of intervention**

Control: standard WHO oral rehydration salts solution

Experimental: oral rehydration salts solution in which glucose (20g/l) was replaced by 50-80g/l of rice powder, the electrolyte concentrations remaining unchanged.

**Types of outcome measures**

- Stool output during the first 24 hours;
- total stool output from admission to cessation of diarrhoea;
- duration of diarrhoea from admission in the study until cessation of diarrhoea;
- weighted estimates of the difference in mean stool output and mean duration between treatment.

**Search strategy for identification of studies**

See: Collaborative Review Group search strategy

The trials register of the Cochrane Infectious Diseases Group (CIDG) was searched for any trial or reference to a relevant trial (published, in-press or in progress). The topic search terms used were: cholera, dehydration, diarrhea (diarrhoea/diarrhea/diarhea), fluid therapy, oral rehydration therapy, oral rehydration solution, rehydration solutions, rice. Full details of the CIDG methods and the journals searched are published in The Cochrane Library in the section on Collaborative Review Groups.
The reviewer searched The Cochrane Controlled Trials Register, published on The Cochrane Library. This is a compilation of about 160,000 published trials identified by hand-searching by various individuals within The Cochrane Collaboration. Full details of the sources and methods used are published in The Cochrane Library. The following databases were also searched: MEDLINE 1966-1998; EMBASE 1988-1998; LILACS, using the search strategy defined by the Cochrane Collaboration, and detailed in appendix 5c of The Cochrane Handbook. The specific topic search terms used were: cholera, dehydration, diarrhea (diarrhoea/diarrhea/diarhea), fluid therapy, oral rehydration therapy, oral rehydration solution, rehydration solutions, rice.

Dates of latest searches:
Cochrane Infectious Diseases Group Trials Register: June 1998
The Cochrane Library: June 1998
MEDLINE: June 1998

Organisations and individual researchers working in the field were contacted for unpublished data, confidential reports and raw data of published trials.

The reviewers also checked the citations of existing reviews and of all trials identified by the above methods.

The external referees were asked to check the completeness of the search strategy and the efforts made to identify unpublished, on-going and planned trials.

Methods of the review

Each trial report was reviewed independently by a statistician and a clinician to determine patient eligibility according to stated selection criteria for age and dehydration status; the number of patients who were randomized and the number of these subsequently excluded from analysis; details of the randomization procedure; and the precise timing of the outcome measurements, such as stool output and intake of oral rehydration salts solution.

In studies where outcomes were presented in two subgroups (patients with Vibrio cholerae isolated from the stool, and those where it was not), mean values were combined as a weighted average, to make them comparable with other studies. The highest standard deviation of the two subgroups was taken.

For studies in children, data from girls were excluded because of the difficulty in measuring precisely stool volumes in female children.

Description of studies

Twenty two studies met the inclusion criteria. All were hospital-based clinical trials.

Studies in patients with cholera were conducted in three countries, Bangladesh (3 studies in children with cholera and 2 studies in adults), Indonesia (1 study in children with cholera and 2 studies in adults), and India (1 study in children with cholera). All studies in patients with cholera only included patients with severe dehydration.

A total of 7 clinical trials were conducted in Bangladesh, of which 5 were either directed conducted or supervised by Dr AM Molla.

Studies in children with non-cholera diarrhoea were conducted in Asia (Bangladesh, India and Pakistan), Mexico, South America (Chile and Peru), and Africa (Egypt). All studies except two (Mexico and Pakistan) only included children above 4-6 months of age. The studies conducted in Mexico and Pakistan only included patients below 6 month of age to assess the digestibility of rice ORS in this age group.

Eight studies were developed during various proposal development workshops organised by the WHO, and therefore used a standardized design and similar data collection forms: Bhan 1987,

Methodological quality
Of the 22 studies, concealment of allocation was adequate in 15. The rest were described as randomized, but details of the method and of any concealment were not given. Patients should have been randomized immediately before treatment with oral rehydration salts solution was started, and after completion of any intravenous treatment for severe dehydration. However, no trial reported when patients with severe dehydration were randomized and outcome measurement initiated - that is, before or after initial intravenous therapy. Thus it was unclear whether the first 24 hour measurement of stool whether the first 24 hour measurement of stool output began when intravenous rehydration was started or when oral rehydration salts solution was first given, as should have been the case.

In one study patients were randomized irrespective of age, but were stratified into arbitrary age groups during analysis (Molla 1985). Ideally, such stratification should have been part of the randomization plan. Stratification during analysis was also done in two other studies (Mochtar 1989, Alam 1987), but this was based on aetiology and so was unavoidable.

Pragmatic analysis according to intention to treat requires that all randomized patients continue to be monitored and that their data be included in the analysis. Nevertheless, in six trials (Guiraldes 1985(a), Patra 1982, Molla 1985, Alam 1987, Mohan 1988, El Mougi 1988) 1-15% of randomized patients were excluded from the analysis, either because they were considered “treatment failures” (usually because additional intravenous treatment was required) or because they had been randomized in error. In two trials that used permuted blocks (Molla 1989) or factorial design (Alam 1992) it seems that some patients were randomized but not reported on, as the numbers specified in the different groups differed appreciably. The reasons for these differences were not stated.

Results
All studies reported stool output and oral rehydration salts solution intake during the first 24 hours. Only a few reported total stool output until diarrhoea stopped, and only a few reported the duration of diarrhoea. Our analysis therefore focused largely on stool output during the first 24 hours. Whether the data were for adults with cholera or with cholera-like diarrhoea, children with cholera or cholera-like diarrhoea, or children with non-cholera diarrhoea, the ratios of mean to standard deviation for stool output were roughly constant, averaging 1.6 and ranging from 1.2 to 2.5. This regularity indicates the need for logarithmic transformation; however, only some of the most recently completed studies reported calculations on that scale. This finding provides a criterion for judging the internal consistency of key outcome data.

In children and in adults with cholera or cholera-like diarrhoea, the mean 24 hour stool output was significantly reduced in those treated with rice ORS compared to those treated with standard WHO ORS.

However, in children with non-cholera diarrhoea the analysis shows that rice ORS caused only a small, statistically non significant, reduction in mean 24 hour stool output.

Summary of analyses
MetaView: Tables and Figures
The figures and graphs in Cochrane Reviews display the Peto Odds Ratio and the Weighted Mean Difference by default. These are not always the methods used by reviewers when combining data in their review. You should check the text of the review for a description of the statistical methods used.

Discussion
Irrespective of age, patients with cholera who were given rice oral rehydration salts solution had substantially lower rates of stool loss than those who were given WHO oral rehydration salts solution in the first 24 hours.
One biological explanation for this is that a greater amount of glucose (and amino acids) is released when rice powder is fully digested than is present in the WHO solution. Assuming that glucose-facilitated absorption of sodium proceeds on an equimolecular basis, 50-80g/l of rice powder would release sufficient glucose and amino acids to promote the absorption of all the sodium (and water) in the rehydration solution and, in addition, reabsorption of at least part of the sodium (and water) secreted into the bowel as part of the diarrhoeal process, thus diminishing stool output. In contrast, the WHO solution contains only enough glucose (20g/l) to promote the absorption of the sodium and water in the solution, thus leaving the rate of stool loss essentially unaffected. The lower osmolarity of the rice solution (about 200 mmol/l vs 310 mmol/l) would also enhance the intestinal absorption of water, but not of sodium.

To take this explanation further, the lack of effect of rice ORS in children with non-cholera diarrhoea when compared to standard WHO ORS could reflect the benefit of feeding immediately after rehydration, providing large amounts of carbohydrates and amino acids, and thus hiding any benefit the additional carbohydrates (and amino acids) contained in the rice ORS might have had.

Reviewers’ conclusions
Implications for practice
Rice oral rehydration salts solution may be more clinically effective for patients with cholera than of WHO standard ORS. This conclusion is based on stool outputs within the first 24 hours. Rice oral rehydration salts have no advantage over standard ORS in children with non-cholera diarrhoea. At least 95% of all cases of diarrhoea in children fall into this category in developing countries. Thus rice oral rehydration salts solution, which is more expensive, is not justified in these groups. Food given immediately after rehydration is generally recommended in these groups.

Implications for research
The results from this systematic review contrast with reports of more promising effects of reduced osmolarity glucose-based ORS, where reduced requirements for supplemental infusion and decreased stool output have been reported. It may be more appropriate to pursue this evidence in reduced osmolarity glucose-based ORS as this appears to be more promising than rice-based ORS. A systematic review of reduced osmolarity ORS against standard ORS is required.

Potential conflict of interest
We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

Characteristics of included studies
Table: Characteristics of included studies
Characteristics of excluded studies
Study : Bhattacharya 1995
No 24 hour output; total stool output not compatible with hospitalised cholera patients.
Study : Cohen 1995
This study is not using rice ORS. The experimental solution tested in this study does not contain rice but some type of carbohydrates obtained by the hydrolysis of rice usually called “glucose syrup solids”. However, in this study the authors called it “rice syrup solids”.
Study : Haider 1994
The population evaluated (diabetic patients) is quite different from the population of interest (childhood diarrhoea or cholera) in this review. It was felt that the two types of diarrhoea had little in common.
Study : Jirapinyo 1996
This study is not using rice ORS. The experimental solution tested in this study does not contain rice but some type of carbohydrates obtained by the hydrolysis of rice usually called “glucose syrup solids”. However, in this study the authors called it “rice syrup solids”.
Study : Kenya 1989
The ratio mean/sd is totally out of range when compared with other studies. The problem here is similar to that of the Mustafa 1995 study.

Study : Khin Maung U 1986
In this study the authors compared standard WHO ORS solution with standard WHO ORS plus “boiled rice feeding”. No group was given rice based ORS solution.

Study : Lebenthal 1995
This study is testing a chemical (amylite) that hydrolyses large quantities of rice into glucose or short chain carbohydrates. The final ORS obtained by this procedure contains essentially glucose.

Study : Mehta 1986
This is not a randomized study. In addition, the three outcome variables measured in the study (stool frequency, volume of stool expressed as large, moderate and small, duration of stay) cannot be compared with the outcome variables from the other studies.

Study : Molina 1995
The rice ORS evaluated in this study only contains 37 g/l of rice.

Study : Molla 1989a
Ratio of mean stool output per standard deviation was very high, incompatible with normal biological variation.

Study : Molla 1989b
No treatment group received rice based ORS.

Study : Mota-Hernandez 1991
The authors just gave rice water, without any salts, to patients who were significantly dehydrated. So the solution is not rice ORS. In addition, this study raises a number of ethical issues, because the patients admitted to this study received less than adequate treatment.

Study : Murtaza 1987
The rice based ORS solution evaluated in this study contained only 30g/l of rice. In addition, the study was not randomized and the ratio stool output/SD is much larger than those reported in other studies.

Study : Mustafa 1995
The ratio mean/sd for stool output is out of range with the other studies. Usually the ratio is very close to one. In this study the standard deviation is very small, much smaller than in any other such study. On the other hand, the ratio mean/sd for ORS intake is what is usually reported, suggesting that ORS intake was well measured, but that the authors had some difficulties in measuring stool output accurately.

Study : Pizarro 1991
No treatment group received rice based ORS.

Study : Prasad 1993
The two outcome variables reported in this article are stool frequency and volume of ORS consumed.

Study : Santosham 1990
The complicated design of this study makes it impossible to clearly identify a control group and a study group.

Study : Wall 1997
The electrolyte content of the rice ORS as well as the control glucose ORS differs significantly from the electrolyte content of the standard WHO ORS solution.

References
References to studies included in this review
Alam 1987 {published data only}

Alam 1992 {published data only}

Bhan 1987 {published data only}

Chea-Woo 1994 {unpublished data only}

Dutta 1988 {published data only}

El Mougi 1988 {published data only}

El Mougi 1991
El Mougi 1991 {unpublished data only}

Faruque 1994a {unpublished data only}
Faruque ASG, Mahalanabis D. Role of rice ORS in infants and young children with acute watery diarrhoea: a randomized controlled clinical trial. Unpublished report.

Faruque 1994b {unpublished data only}
Faruque ASG, Mahalanabis D. Role of rice ORS in infants and young children with acute watery diarrhoea: a randomized controlled clinical trial. Personal communication.

Fayad 1993 {published data only}

Guiraldes 1995a {published data only}

Guiraldes 1995b {published data only}

Islam 1994 {published data only}
Maulen 1994 {published data only}

Mochtar 1989 {unpublished data only}
Personal communication.

Mohan 1988 {published data only}

Molla 1983 {published data only}

Molla 1985 {published data only}


Molla 1994 {unpublished data only}

Northrup 1992 {unpublished data only}

Patra 1982 {published data only}

Razafindrakoto 1993 {published data only}

* indicates the major publication for the study

References to studies excluded from this review
Bhattacharya 1995
Cohen 1995
Haider 1994

Jirapinyo 1996


Kenya 1989


Khin Maung U 1986


Lebenthal 1995


Mehta 1986


Molina 1995


Molla 1989a


Molla 1989b


Mota-Hernandez 1991


Murtaza 1987


Mustafa 1995


Pizarro 1991


Prasad 1993

Santosham 1990

Wall 1997

Previously published versions
Gore 1992

Gore 1996

Coversheet
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Extramural sources of support to the review
Department for International Development UK
European Commission (Directorate General XII) BELGIUM
Intramural sources of support to the review
World Health Organisation SWITZERLAND
Synopsis

Synopsis pending
Comments and criticisms
Survey of Cochrane Library 1998.4
Summary of comments and criticisms
Thank you for an informative review on an important topic. We have some minor suggestions to help make the review clearer in some sections.

BACKGROUND/TYPES OF OUTCOMES
The rate of stool loss is mentioned in the background but not >selected as an outcome. An explanation of why this is so would be helpful.

METHODS OF THE REVIEW
It would be helpful to have a description of how the data were >synthesized and whether heterogeneity was tested.

RESULTS
Under Methodological quality of included studies, the reviewers >state that intention to treat analysis was not performed in some of the trials and that some dropouts were treatment failures. We would like to see a subgroup analysis including only trials which reported on all randomised participants, to see if the overall results were different.

CONCLUSIONS
We acknowledge the short follow up period of 24 hours reported in most trials, and suggest that the reviewers might recommend a longer follow up in the “implications for research” or explain why longer follow up is not clinically important. We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of our criticisms.

Reviewer’s reply

BACKGROUND/TYPES OF OUTCOMES
The expression “rate of stool loss” should be deleted. The sentence in the background section will be modified in the next revision to read as follows: “It neither reduces stool loss nor shortens duration...”

METHODS OF THE REVIEW
The data were either from (i) published articles, or (ii) original data from individual studies available for meta-analysis Heterogeneity was not tested.

RESULTS
In studies conducted on patients with cholera, removing the studies that did not perform “intention to treat analysis” would mean removing 3 out of 4 studies conducted in adults, and 1 out of 4 studies conducted in children. However, as all studies conducted in patients with cholera show a reduction in stool loss in patients treated with rice ORS, removing these 4 studies that did not perform “intention to treat analysis” would not change the overall direction of the conclusion but might change weight of evidence. For studies conducted in patients with acute non-cholera diarrhoea, 3 studies out of 15 did not perform an intention to treat analysis”. These three studies represent a total weight of about 5%. In this case again, removing these studies does not change the overall conclusion of the meta-analysis (the reduction in stool loss in the first 24 hours in patients treated with rice ORS goes from 4.3g/kg to 3.1 g/kg).

CONCLUSIONS
Based on previous studies conducted on patients with acute diarrhoea, we can estimate that stool loss in the first 24 hours after admission represent 70% of total stool loss after admission. In the second 24 hours after admission, stool loss represent 20% of the total stool loss, and in the third 24 hour period after admission, the stool loss represent 10% of the total stool loss (Madkour AM et al. Journal of Pediatric Gastroenterology and Nutrition, 1993; 17:176-181). From this, it is clear that the most important period for an “improved ORS solution” to show a clinically significant impact on stool output is the first 24 hour period after admission in the study.

Contributors to comment

The above comment was made as part of a collaborative effort coordinated by Ole Olsen at the Nordic Cochrane Centre. All new reviews on Cochrane Library 1998.4 were selected and critically read by a set of methodologists, comments were coordinated and finally fed back. The general results of the survey will be presented at the Cochrane Colloquium in Rome, October 1999. We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of our criticisms.

Jeanette Ezzo and Jos Kleijnen

Nate Pierce study

Summary of comments and criticisms

Regarding the Nate Pierce study, while it is true that there are not clinically significant results with rice-based ORS except (to date) with cholera, it is also true that most rice-based ORS show at least 17% better hydration in non-cholera ORS and rice-ORS is better accepted, can be served warm as well as cold, and never increases fluid losses, as may be the case sometimes with glucose ORS.

Reviewer’s reply

Comment 1: “while it is true that there are not clinically significant results with rice-based ORS except (to date) with cholera, it is also true that most rice-based ORS show at least 17% better hydration in non-cholera ORS”

Reply: In none of the studies we reviewed was “hydration” mentioned as an outcome variable. We are not aware of a direct randomized comparison demonstrating that “most rice ORS show at least 17% better hydration in non-cholera ORS”. What is the definition of “better hydration” and how was it measured and in which studies?

Comment 2: “rice-ORS is better accepted, can be served warm as well as cold”

Reply: The review concentrates on clinically relevant endpoints (i.e., stool output and duration of diarrhoea) and did not include a systematic comparison of acceptability qualities mentioned in Ms Riikonen’s comments.

Comment 3: “[rice-ORS] never increases fluid losses, as may be the case sometimes with glucose ORS”

Reply: Fluid losses can be increased with the use of ORS containing glucose polymers as shown by Dr El-Mougi (El-Mougi M et al. Efficacy of standard glucose based and reduced osmolarity maltodextrin based oral rehydration solutions: effect of sugar malabsorption).

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Keywords