Reduced osmolarity oral rehydration solution for treating cholera (Review)

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Reduced osmolarity oral rehydration solution for treating cholera

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A B S T R A C T

Background
Oral rehydration solution (ORS) is used to treat dehydration caused by diarrheal diseases including cholera. Reduced osmolarity formulations are safe and more effective than standard ORS for treating non-cholera diarrhea. As cholera causes rapid electrolyte loss, it is important to know if these benefits are similar for people with cholera.

Objectives
To compare the safety and efficacy of reduced osmolarity oral rehydration solution (ORS) with standard ORS for treating diarrhea due to cholera.

Search strategy
We searched the Cochrane Infectious Disease Group Specialized Register (January 2004), CENTRAL (The Cochrane Library Issue 1, 2004), MEDLINE (1966 to January 2004), EMBASE (1974 to January 2004), and LILACS (1982 to January 2004). We also contacted organizations and searched reference lists.

Selection criteria
Randomized controlled trials comparing reduced osmolarity ORS with standard ORS for treating adults and children with acute diarrhea due to cholera.

Data collection and analysis
Two reviewers independently applied eligibility criteria, assessed trial quality, and extracted data. We pooled binary data using risk ratios (RR), continuous data using mean difference (MD) or the standardized mean difference (SMD), and presented the results with 95% confidence intervals (CI).

Main results
For glucose-based reduced osmolarity ORS, seven trials (718 participants) met the inclusion criteria. Biochemical hyponatremia (serum sodium < 130 mmol/L) was more common with reduced osmolarity ORS (RR 1.67, CI 1.09 to 2.57; 465 participants, 4 trials); for severe biochemical hyponatremia (serum sodium < 125 mmol/L) this was not significant (RR 1.58, CI 0.62 to 4.04; 465 participants, 4 trials).
No trials reported symptomatic hyponatremia or death. We found no statistically significant difference in the need for unscheduled intravenous infusion. Analyses separating children and adults showed no obvious trends.

Two trials also examined rice-based ORS. In the reduced osmolarity group, duration of diarrhea was shorter (MD -16.85 hours, CI -21.22 to -12.48; 102 participants, 2 trials).

**Authors’ conclusions**

In people with cholera, reduced osmolarity ORS is associated with biochemical hyponatremia when compared with standard ORS, although there are similar benefits in terms of other outcomes. Although this risk does not appear to be accompanied by serious consequences, the total patient experience in existing trials is small. Under wider practice conditions, especially where patient monitoring is difficult, caution is warranted.

**PLAIN LANGUAGE SUMMARY**

In people with cholera, reduced osmolarity oral rehydration solution (ORS) is associated with low blood salt levels but no life-threatening clinical effects

Cholera is caused by bacteria ingested through contaminated food or water and is commonly found where sanitation measures are poor. It causes severe diarrhea and vomiting, which can lead to profound dehydration and potentially death. ORS is an effective treatment for diarrhea, but a new ORS with a lower electrolyte content is safe and more effective in people with non-cholera diarrhea. This review found that this new ORS appears to be as effective as the original formula in people with cholera, but may lead to low blood salt levels. More research is needed to better understand these potential safety issues.

**BACKGROUND**

Cholera, one of the most serious types of infectious diarrheal disease, inflicts severe social and economic hardship in outbreak areas (WHO 2001a). In 2001, 58 countries reported 184,311 disease episodes and 2728 deaths, with the reported numbers thought to represent only 5 to 10 per cent of actual cases (WHO 2003). Caused by ingesting food or water containing the bacterium *Vibrio cholerae*, the disease can spread rapidly among populations lacking access to safe water and adequate sanitation facilities. Upon infection of the small intestine, the bacteria produce a protein enterotoxin that induces hypersecretion of water and electrolytes by the small intestinal mucosa. Symptoms of cholera include acute watery diarrhea, vomiting, and severe dehydration, which can lead to death within 24 hours if left untreated (Sack 2004).

Oral rehydration solution (ORS) was developed in the late 1960s. It is an important intervention for reducing morbidity and mortality associated with diarrheal disease, regardless of etiology (WHO 2000). ORS has been highly effective in reducing the high mortality rates experienced during cholera outbreaks, which often reached 50 per cent before the introduction of this treatment (Quotah 1999). Utilizing a simple and inexpensive solution of sodium and glucose, ORS enhances sodium and fluid absorption in the small intestine, even in cases of enterotoxic diarrhea where fluid loss is often substantial.

A standard formulation of ORS consists of 90 mmol/L of sodium, 20 mmol/L of potassium, 80 mmol/L of chloride, 10 mmol/L of citrate, 111 mmol/L of glucose, with a total osmolarity of 311 mmol/L. Initially estimated to replace sodium losses in adults with cholera, this formulation was until recently recommended (and is still considered acceptable) by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) for treating all types of diarrhea in children and adults (Rabban 2000; WHO 2001b; WHO 2002). Even though the expanded use of this solution has saved millions of lives, its optimal composition remains an issue of debate (Duggan 2004; Guarino 2000; Nalin 2004).

Potential problems with the standard ORS formulation are that it may not lower stool output or duration of diarrhea, which reduces its acceptance in many communities (Rabban 2000). Alternative
formulations, including those that use lower electrolyte concentrations or replace glucose with complex carbohydrates such as rice powder, or both, have been introduced with the aim of reducing osmolarity to promote greater salt and water absorption in the small intestine. In a recent systematic review, reduced osmolarity ORS was found to be safe and more effective when compared with standard ORS for treatment of diarrhea in children (Hahn 2001). Acknowledging the benefits of reduced osmolarity ORS solutions, WHO and UNICEF now recommend that countries use and manufacture formulations with a total osmolarity of 245 mmol/L (WHO 2001b). However, there are concerns about potential adverse effects of a reduced osmolarity solution in people with cholera (Hahn 2001; Nalin 2004; WHO 2001b). Because cholera is associated with significant electrolyte loss especially among children, the use of ORS with reduced sodium levels may place patients at a greater risk for developing biochemical hyponatremia (low blood sodium levels < 130 mmol/L) (Fuchs 2001), which can result in severe illness including seizures, respiratory arrest, coma (symptomatic hyponatremia), and even death. In areas where cholera is endemic, practitioners will therefore require the best available evidence about the balance between the benefits and risks of different ORS formulations.

OBJECTIVES

To compare safety and efficacy of reduced osmolarity with standard oral rehydration solution for treating diarrhea due to cholera.

METHODS

Criteria for considering studies for this review

Types of studies
Randomized controlled trials.

Types of participants
Adults and children with acute diarrhea confirmed (by stool microscopy or stool culture) or presumed to be caused by V. cholerae.

Types of interventions

Intervention
Reduced osmolarity ORS (total osmolarity (250 mmol/L with reduced sodium).

Control
Standard ORS formulation (sodium 90 mmol/L, glucose 111 mmol/L, total osmolarity 311 mmol/L).

Types of outcome measures

Primary
- Need for unscheduled intravenous infusion.
- Symptomatic hyponatremia as defined by trialists (symptoms include headache, lethargy, confusion, and seizures).

Secondary
- Biochemical hyponatremia as defined by trialists.
- Duration of diarrhea.
- Stool volume in first 24 hours after admission or randomization.
- Vomiting during rehydration.
- Death.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1. Cochrane Infectious Diseases Group’s Specialized Register (January 2004); Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library (Issue 1, 2004); MEDLINE (1966 to January 2004); EMBASE (1974 to January 2004); and LILACS (1982 to January 2004).

Organizations

We provided individuals from the following key agencies and organizations with a list of trials identified and asked for additional completed or ongoing trials: World Health Organization; Centre for Health and Population Research (ICDDR,B); Jawaharlal Nehru Medical College; National Institute of Cholera and Enteric Diseases, India; All India Institute of Medical Sciences; and the U.S. Naval Medical Research Unit, Jakarta.
Reference lists
We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis
We planned the following analyses, but they were not required with the trials available; we will use them if required when we add new trials to the review: (1) analysis of geometric means and standard deviation using log normal approximation; (2) analysis of time-to-event or censored data, when available, to estimate the log hazards ratio and its variance within each trial, using methods proposed by Parmar 1998; (3) examination of funnel plots for asymmetry indicative of publication bias; and (4) sensitivity analysis to determine the degree to which the results were influenced by the adequacy of allocation concealment.

Selection of studies
We screened the results of the search to select potentially relevant studies. Colleen Murphy (CM) and Jimmy Volmink (JV) independently applied the inclusion criteria, based on the type of participant, study design, intervention, and comparisons. We resolved differences in opinion through discussion with Seokyang Hahn (SH). Where there was ambiguity, we sought clarification from the trial authors and reassessed the articles. We excluded studies that did not meet these criteria and stated the reasons in the 'Characteristics of excluded studies'.

Data extraction and management
Using a specially designed data extraction form, CM extracted information on methods, participants, interventions, and outcomes from each trial, and SH independently extracted the outcome data and the information on trial and participant characteristics. CM entered the data into Review Manager 5. We scrutinized data sources for multiple publications from the same data sets, and where there were differences, we referred to the original paper. We extracted the number of participants randomized in each group and the numbers analyzed for each outcome. For binary data we extracted the number of events and for continuous data the mean and standard deviation or information to estimate the standard deviation.

Assessment of risk of bias in included studies
We independently assessed the methodological quality of the included trials using the following criteria.
1. Generation of allocation sequence: judged as 'adequate' if methods such as table of random numbers, computer-generated random numbers, or coin tossing were used.
2. Concealment of allocation: judged as 'adequate' if methods such as central randomization and sequentially numbered, sealed, opaque envelopes were used.
3. Blinding: we recorded whether investigators, participants, or assessors were blinded.
4. Inclusion of all randomized participants: we recorded the percentage of randomized participants included in the analysis in each trial.

When necessary, we contacted trial authors for clarification.

Data synthesis
We analyzed data for glucose-based and rice-based reduced osmolarity ORS separately using Review Manager 5. We pooled estimates of effect using risk ratios (RR) for binary data and mean difference (MD) for continuous data; and presented these results with 95% confidence intervals (CI). For continuous outcome data that were expressed in different units, we calculated standardized mean difference (SMD).

We assessed heterogeneity by visually examining the forest plot and using the chi² test (using a 10% level of significance) and the I² statistic (Higgins 2003). In the absence of homogeneity of treatment effects, we used a random-effects model. We investigated clinical heterogeneity based on the age of participants by comparing children (< 10 years) with adults, as children may be particularly at risk for developing hyponatremia.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Trial selection
We identified 12 studies that appeared to meet our inclusion criteria and are aware of two ongoing trials (see 'Characteristics of ongoing studies'). However, we excluded five studies because one did not evaluate people with cholera, two did not administer reduced osmolarity or standard ORS, one did not employ randomization, and one reported cholera and non-cholera data in aggregate only (see 'Characteristics of excluded studies').
The seven randomized controlled trials included in the analysis were small in size or only included a small subset of participants with cholera, with a combined sample size of 797 participants. We included data from an unpublished trial (Punjabi 1995), and the remaining six trials were published in English-language biomedical journals. We have provided details of these trials in the '
Characteristics of included studies’ and have summarized them below.

Participants and location
All trials, including one multicenter trial (Choice 2001), were conducted in low-income countries: Bangladesh (Alam 1999; Choice 2001; Faruque 1996), Brazil (Choice 2001), India (Alam 1999; Alam 2000; Choice 2001; Dutta 2000), Indonesia (Choice 2001; Punjabi 1995), Peru (Choice 2001), and Vietnam (Choice 2001). The majority of participants were adults, but three trials (151 participants) assessed children with cholera (Alam 2000; Choice 2001; Dutta 2000). Five trials included only or predominantly male participants. All trial participants were suffering from a severe degree of dehydration.

Interventions
While all seven trials compared glucose-based, reduced osmolarity ORS with the standard ORS formula, two trials also included an experimental rice-based, reduced osmolarity ORS trial arm (Bhattacharya 1998; Dutta 2000); the formulations are detailed in Appendix 2.

Before randomization, six trials administered intravenous rehydration solutions such as Ringer’s lactate, Dhaka solution, or saline solution to correct severe dehydration (Alam 1999; Bhattacharya 1998; Choice 2001; Dutta 2000; Faruque 1996; Punjabi 1995). Five trials treated all participants with antibiotics (Alam 1999; Alam 2000; Bhattacharya 1998; Dutta 2000; Faruque 1996), with a sixth administering an antibiotic if an intercurrent infection occurred (Choice 2001).

Three trials discussed feeding (Alam 1999; Alam 2000; Choice 2001). Alam 1999 gave participants bread and bananas immediately after rehydration and standard meals three times daily thereafter. Children in Alam 2000 were fed curds and bread upon improvement of rehydration and breastfeeding was continued throughout. In Choice 2001, breastfeeding was also continued ad libitum and food appropriate to age was given to children during the maintenance phase. The four remaining trials did not report information on feeding.

Outcomes
The trials assessed the following pre-specified outcomes used in this review: need for unscheduled intravenous infusion, biochemical hyponatremia, duration of diarrhea, stool volume in first 24 hours after admission or randomization, and vomiting during rehydration. Many of these indicators were measured at different time points. They also assessed other outcomes, which are described in the ‘Characteristics of included studies’.

None of the trials assessed symptomatic hyponatremia and death as pre-specified outcomes, although the incidence of clinical signs associated with hyponatremia was either mentioned in the manuscript text or obtained through correspondence with trialists for four trials (Alam 1999; Choice 2001; Dutta 2000; Faruque 1996). Information on death was reported in the manuscript text of Bhattacharya 1998 and obtained by correspondence with the Choice 2001 trialists.

We contacted the trial authors if the published reports did not include the outcomes assessed in this review; we received unpublished outcome data for Choice 2001 and Punjabi 1995.

Risk of bias in included studies

Generation of allocation sequence
All trials were reported as randomized. Five trials employed permuted block randomization for generating the allocation sequence, which we considered an adequate method (Alam 1999; Bhattacharya 1998; Choice 2001; Dutta 2000; Faruque 1996); however, these trials did not explicitly mention how the sequence was generated. The other two trials did not state how they generated the allocation sequence.

Allocation concealment
Five trials did not describe methods used to conceal allocation. Two trials reported that randomized allocations were incorporated into serially numbered boxes or packets of ORS sachets, which we considered an adequate method (Alam 2000; Faruque 1996).

Blinding
Four trials reported that both participants and providers were blinded to treatment assignment (Alam 1999; Alam 2000; Choice 2001; Punjabi 1995). Blinding methods were unclear in the other three trials.

Inclusion of all randomized participants
None of the trials reported the number of participants lost to follow up, and in each trial all randomized individuals were included in the final analysis.

Effects of interventions

Reduced osmolarity (glucose-based) ORS versus standard ORS
Of the seven trials (718 participants) that evaluated reduced osmolarity (glucose-based) ORS, three assessed only children (< 10
years; n = 132), and four evaluated only adults (> 15 years; n = 586).

**Need for unscheduled intravenous fluid infusion (Analysis 1.1)**

While there was tendency towards a reduction in unscheduled intravenous infusion for those administered reduced osmolarity (glucose-based) ORS, this finding was not statistically significant (RR 0.86, CI 0.66 to 1.12; n = 616, 5 trials).

**Symptomatic hyponatremia**

No instances of symptomatic hyponatremia were reported in the four trials that assessed this outcome (Alam 1999; Choice 2001; Dutta 2000; Faruque 1996).

**Biochemical hyponatremia (Analysis 1.2 and Analysis 1.3)**

Those receiving reduced osmolarity ORS were almost 70% more likely to develop biochemical hyponatremia (defined as serum sodium < 130 mmol/L) (RR 1.67, CI 1.09 to 2.57; n = 465, 4 trials).

Although the point estimate for severe biochemical hyponatremia (defined as serum sodium < 125 mmol/L) was in the same direction, the result was statistically inconclusive with a wide confidence interval (RR 1.58, CI 0.62 to 4.04; n = 465, 4 trials).

**Duration of diarrhea (Analysis 1.4)**

We found no statistically significant difference in the duration of diarrhea between the two groups (MD -1.08, CI -4.58 to 2.41 hours, random-effects model; n = 718, 7 trials). We detected substantial heterogeneity between the trials (chi² = 20.97, df = 6, P = 0.002; I² = 71.4%).

**Stool volume in first 24 hours after admission or randomization (Analysis 1.5)**

We found no statistically significant difference in the stool volume in the first 24 hours between the two groups (SMD -0.13, CI -0.43 to 0.17, random-effects model; n = 511, 4 trials). We detected substantial statistical heterogeneity between the trials (chi² = 8.21, df = 6, P = 0.04; I² = 63.4%). The heterogeneity appears to be attributable to the one trial that demonstrated a statistically significant benefit in favor of the reduced osmolarity formula (Faruque 1996); the sodium content of the reduced osmolarity formula in this trial was lower than that of the other trials.

**Vomiting during rehydration (Analysis 1.6)**

The proportion of people that vomited during rehydration was similar in the two groups (RR 1.14, CI 0.92 to 1.40; n = 363, 2 trials).

**Death**

No deaths were reported in the two trials that assessed mortality (Bhattacharya 1998; Choice 2001).

**Exploring heterogeneity: children (< 10 years) versus adults (Analysis 1.1 to Analysis 1.6)**

When we conducted subgroup analyses assessing children and adults separately, there appeared to be differences in the direction of treatment effect estimates for most outcomes. However, as the overall numbers of children were small and the confidence intervals tend to include both point estimates with some degree of overlap, it is difficult to determine whether these represent true differences. While the strength of treatment benefit for the outcome ‘need for unscheduled intravenous infusion’ appeared to be greater in children (RR 0.57, CI 0.29 to 1.11; n = 93, 2 trials) than adults (RR 0.93, CI 0.70 to 1.24; n = 523, 3 trials) receiving reduced osmolarity (glucose-based) ORS, the point estimate for children has a wide confidence interval and is not statistically significant at the predefined five per cent level. Biochemical hyponatremia may be more problematic for adults receiving the reduced osmolarity formula (RR 1.69, CI 1.06 to 2.69; n = 426, 3 trials), yet this outcome for children was assessed in only one small trial with few events, resulting in a wide confidence interval and lack of statistical significance (RR 1.58, CI 0.53 to 4.74; n = 39). For the two diarrheal outcomes where statistically significant heterogeneity was evident, heterogeneity in adults persisted in the subgroup analysis.

**Reduced osmolarity (rice-based) ORS versus standard ORS**

Two trials (102 participants) evaluated reduced osmolarity (rice-based) ORS.

**Need for unscheduled intravenous fluid infusion**

No information available.

**Symptomatic hyponatremia**

No instances of symptomatic hyponatremia were reported in the one trial that reported on this outcome (Dutta 2000).
Biochemical hyponatremia (Analysis 2.1 and Analysis 2.2)

While the point estimates suggest a reduced risk of biochemical hyponatremia (serum sodium < 130 mmol/L) for those receiving reduced osmolarity (rice-based) ORS, these findings are not statistically significant (RR 0.66, CI 0.26 to 1.69; n = 102, 2 trials). For severe biochemical hyponatremia (serum sodium < 125 mmol/L), the confidence interval around the risk ratio is wide reflecting the small number of events for this outcome (RR 0.35, CI 0.02 to 8.10; n = 102, 2 trials).

Duration of diarrhea (Analysis 2.3)

Duration of diarrhea was statistically significantly reduced for those receiving the reduced osmolarity (rice-based) formula (MD -16.85 hours, CI -21.22 to -12.48; n = 102, 2 trials).

Other outcomes

None of the trials evaluated or reported on the other outcomes of interest.

Exploring heterogeneity: children (< 10 years) versus adults (Analysis 2.1 to Analysis 2.3)

One small trial was available for each subgroup, but there was no statistically significant difference in outcomes between children and adults.

Discussion

Our review draws attention to the paucity of evidence on the effects of reduced osmolarity (glucose-based) ORS compared with standard ORS for people with cholera, with only seven trials evaluating 718 participants.

We intended to examine the safety of reduced osmolarity ORS for cholera by measuring the incidence of symptomatic hyponatremia, as low serum sodium levels may be transient and therefore not necessarily resulting in serious illness. The 2001 WHO/UNICEF meeting of ORS formulation experts highlighted the importance of this outcome in people receiving treatment for cholera (WHO 2001b). As none of the trials found or evaluated symptomatic hyponatremia, we could not assess this outcome. Instead, we measured the incidence of biochemical hyponatremia. Asymptomatic hyponatremia, while not providing a definitive marker for treatment failure, provides an important measure of potential risk for people with cholera.

We found participants receiving low osmolarity ORS to be at greater risk of developing biochemical hyponatremia (serum sodium < 130 mmol/L), but the relatively few cases of severe biochemical hyponatremia (serum sodium < 125 mmol/L) precludes firm conclusions regarding this outcome. These findings should, nevertheless, alert clinicians to the need for vigilance concerning the risk of hyponatremia in non-trial settings.

For other outcomes comprising unscheduled intravenous infusion, stool volume, vomiting, and duration of diarrhea, there was little difference in effect between the two types of formulae. However, as most of the available trials are small with low numbers of events, there may have been insufficient power to demonstrate important clinical differences even after pooling of the results.

In separate analyses of two trials (102 participants) comparing reduced osmolarity (rice-based) ORS with the standard ORS formula, we found no statistically significant differences except for the duration of diarrhea, which was substantially shorter in the group receiving reduced osmolarity (rice-based) ORS. A similar finding was reported in a systematic review that compared rice-based ORS with glucose-based standard ORS formulas in people with diarrhea (Fontaine 1998).

Data available for assessing the new formula’s safety and efficacy in children with cholera are also extremely limited, which makes it difficult to draw a conclusion. Only one trial reported the risk of biochemical hyponatremia in children (Choice 2001), and it showed a trend favoring the standard formula, but this finding was not statistically significant.

WHO and UNICEF currently recommend formulations with a total osmolarity of 245 mmol/L for diarrhea. It is not known, however, whether using ORS with a reduced osmotic load is appropriate in cholera-endemic regions where the balance between benefit and harm can be tenuous. Logistically, having one ORS formula is advantageous. However, the increased risk of biochemical hyponatremia in those receiving low osmolarity solutions is of concern. Even though there were no instances of symptomatic hyponatremia or death, the total patient experience in the trials is very small and these effects cannot be ruled out under wider practice conditions. Moreover, careful monitoring of blood sodium levels may be difficult in areas where healthcare resources are limited, most notably during complex emergencies and large epidemics. Further trials in both adults and children with cholera should be undertaken to clarify these issues.

Authors’ Conclusions

Implications for practice

In people with cholera, reduced osmolarity ORS results in a higher incidence of biochemical hyponatremia with no discernable benefits in terms of the need for unscheduled intravenous infusion, duration of diarrhea, or stool volume compared with the standard formula. The increased risk of low serum sodium levels could have
major implications in resource-constrained settings where clinicians may not have monitoring facilities and must rely on presumptive diagnosis. Although we found no serious clinical consequences related to hyponatremia, it is important to note that the total patient experience in the existing trials is small.

WHO and UNICEF currently recommend a reduced osmolarity ORS formulation for treating dehydration for all types of diarrhea. While it may be easier to administer a single ORS formulation worldwide, the potential harms and limited evidence of improved efficacy for people with cholera should be kept in mind.

**Implications for research**

Further randomized controlled trials are needed to assess the balance between benefit and harm associated with the use of reduced osmolarity ORS in people with cholera. These trials should be large enough to adequately assess important outcomes such as symptomatic hyponatremia and death.

**ACKNOWLEDGEMENTS**

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We wish to thank Paul Garner for his guidance in developing the protocol. We are also grateful to trialists who provided us with clarifications and unpublished data.

**REFERENCES**

References to studies included in this review

- Alam 1999 *(published data only)*

- Alam 2000 *(published data only)*

- Bhattacharya 1998 *(published data only)*

- Dutta 2000 *(published data only)*

- Faruque 1996 *(published and unpublished data)*

- Punjabi 1995 *(published and unpublished data)*
  Punjabi NH, Pulungsih SP, Rifaijai A, Kumala S, O’Hanley P, Simanjuntak CH, et al. A double blind controlled trial comparing...

References to studies excluded from this review

Bhan 1995 [published data only]

Dutta 2001 [published data only]

Fontaine 1998

Fuchs 2001

Guarino 2000

Hahn 2004

Higgins 2003

Nalin 2004

Parmar 1998

Quotah 1999

Rabbani 2000

WHO 2001

WHO 2001a

WHO 2001b


* Indicates the major publication for the study
### Characteristics of included studies  [ordered by study ID]

#### Alam 1999

| Methods | Generation of allocation sequence: permuted blocks of variable length (adequate)  
Concealment of allocation: not stated  
Blinding: participants, providers blinded  
Inclusion of all randomized participants: not stated |
|---|---|
| Participants | Number of participants: 300 randomized (168 men; 131 women)  
Inclusion criteria: adult men and women aged 15 to 55 years; history of acute watery diarrhea for < 24 h before admission; severe dehydration; stool positive for Vibrio cholerae under dark-field illumination; successful rehydration with intravenous infusion within 6 h of admission  
Exclusion criteria: suspected pregnancy; bloody diarrhea; systemic infection requiring intravenous antibiotics; inability to rehydrate with intravenous infusion within 6 h after admission |
| Interventions | 1. Reduced osmolarity (glucose-based)ORS  
2. Standard ORS  
See Appendix 2 for the ORS compositions  
Co-interventions: erythromycin (500 mg orally every 6 h for 3 days)  
Food: bread, banana (immediately after rehydration), and standard meals (rice, fish, or meat, vegetables and lentils) 3 times daily)  
Water: given as desired, usually with meals |
| Outcomes | 1. Need for unscheduled intravenous infusion<sup>a</sup>  
2. Duration of diarrhea (after randomization, h)<sup>a</sup>  
3. Vomiting during rehydration during initial 24 h<sup>a</sup>  
4. Stool volume in first 24 h after admission/randomization<sup>a</sup>  
5. Total stool weight, g/kg body weight  
6. Urine volume during initial 24 h (ml/kg bodyweight)  
7. Total urine volume (ml/kg body weight)  
8. Initial 24 h ORS intake (ml/kg body weight)  
9. Total ORS intake (ml/kg body weight)  
10. Initial 24 h water intake (ml/kg body weight)  
11. Total water intake (ml/kg body weight)  
12. Biochemical hyponatremia (< 130 mmol/L) 24 h after admission<sup>a</sup>  
13. Biochemical hyponatremia (< 125 mmol/L) 24 h after admission<sup>a</sup>  
14. Biochemical hyponatremia (< 120 mmol/L) 24 h after admission<sup>a</sup> |
| Notes | Location: Bangladesh. (Trial started at 2 sites, in Bangladesh and Indonesia, but it was discontinued at the latter due to inadequate participant supervision. No data from Indonesia included in the analysis.)  
Date: July 1995 to May 1997 |
### Alam 2000

**Methods**
- Generation of allocation sequence: not stated
- Concealment of allocation: sachet packets serially given a number by an uninvolved colleague
- Blinding: participant and provider blinded
- Inclusion of all randomized participants: not stated

**Participants**
- Number of participants: 179 randomized (cholera proved by culture in 35)
- Inclusion criteria: all children with acute diarrhea (< 4 days duration) with dehydration that met 1 of the following: non-cholera diarrhea, aged between 3 months and 5 years, children above 3 months with clinical suspicion of cholera
- Exclusion criteria: children with clinical evidence of systemic infection; encephalopathy; electrolyte imbalance; convulsions; invasive diarrhea

**Interventions**
1. Reduced osmolarity (glucose-based) ORS
2. Standard ORS
   - See Appendix 2 for the ORS compositions
   - 75 ml/kg ORS in first 4 h
   - Food: curds and banana feeds offered once hydration improved
   - Co-intervention: single dose of doxycycline (8 mg/kg) administered to all with clinical suspicion of cholera or stool positive for motiles (repeated if vomited within 0.5 h of administration)

**Outcomes**
1. Need for unscheduled intravenous infusion
2. Overall diarrhea frequency (stool/4 h)
3. Overall ORS consumed (L)
4. Overall diarrhea duration
5. Weight gain
6. Caloric intake (kcal/kg/day)
7. Serum sodium (meq/L)
8. Urine output (boys) (ml/kg/h)
9. Intravenous fluids (ml/kg)

**Notes**
- Location: Diarrhea Training and Treatment Unit, Aligarh, India
- Date: unclear

### Bhattacharya 1998

**Methods**
- Generation of allocation sequence: permuted blocks of random numbers of block length 16 (adequate)
- Concealment of allocation: not stated
- Blinding: not stated
- Inclusion of all randomized participants: not stated

**Participants**
- Number of participants: 123 randomized
- Inclusion criteria: adult men; acute watery diarrhea for < 24 h; severe dehydration; severe cholera
- Exclusion criteria: received antibiotics before hospitalization; received intravenous fluid before hospitalization; systemic illness

**Interventions**
1. Reduced osmolarity (glucose-based) ORS
2. Reduced osmolarity (rice-based) ORS
3. Standard ORS
   - See Appendix 2 for the ORS compositions
   - Co-interventions: doxycycline (300 mg) as a single dose after correction of initial dehydration and when vomiting
Outcomes

1. Duration of diarrhea (h)\textsuperscript{a}
2. Total stool output (L)
3. Number (%) of participants with 24-h serum sodium level of 125 to 130 mmol/L\textsuperscript{a}
4. Number (%) of participants with 24-h serum sodium level of > 130 mmol/L\textsuperscript{a}
5. Total ORS intake (L)
6. Body weight increment (%)
7. Total fluid requirement (L)

Notes
Location: Infectious Diseases Hospital, Calcutta India
Date: August 1993 to March 1996

Choice 2001

Methods
Generation of allocation sequence: permuted blocks of variable length (adequate)
Concealment of allocation: not stated
Blinding: participant and provider blinded
Inclusion of all randomized participants: not stated

Participants
Number of participants: 675 randomized (58 with cholera)
Inclusion criteria: male children aged 1 to 24 months; diarrhea for < 72 h (with passage of 3 or more watery stools in the 24 h before admission); signs of some or severe dehydration
Exclusion criteria: bloody diarrhea; clinical signs of systemic infection that required intravenous antibiotic therapy; severe malnutrition defined as admission weight for height < 65% of the National Center for Health Statistics standard (to account for rehydration); presence of obvious edema

Interventions
1. Reduced osmolarity (glucose-based)ORS
2. Standard ORS
See Appendix 2 for the ORS compositions
Co-interventions: breastfeeding ad libitum; food appropriate for age during maintenance phase; water ad libitum during maintenance phase; antibiotics if developed intercurrent infections after enrollment

Outcomes
1. Stool output (g/kg) at 24 h\textsuperscript{a}
2. Total stool output (g/kg)
3. ORS intake (ml/kg) at 24 h
4. Total ORS intake (ml/kg)
5. Vomiting in first 24 h (%)
6. Vomitus 10 g/kg (%)
7. Unscheduled intravenous therapy in first 24 h (%)\textsuperscript{a}
8. Children with serum sodium at 24 h (%): < 130 mmol/L; < 125 mmol/L\textsuperscript{a}
9. Duration of diarrhea\textsuperscript{a}

Notes
Location (5 centers):
1. Centre for Health and Population Research, Bangladesh (ICDDR,B)
2. Centro Pediatrico Professor Hosannah de Oliveira-Universidade Federal da Bahia, Salvador, Brazil
3. All India Institute of Medical Sciences and Kasturba Hospital, New Delhi, India
4. Hospital Nacional Cayetano Heredia, Lima, Peru
Choice 2001  (Continued)

<table>
<thead>
<tr>
<th>5.</th>
<th>Children’s Hospital No. 1, Ho Chi Minh City, Vietnam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: June 1995 to February 1997</td>
<td></td>
</tr>
</tbody>
</table>

**Dutta 2000**

**Methods**
- Generation of allocation sequence: permuted blocks of random numbers of block length 9 (adequate)
- Concealment of allocation: not stated
- Blinding: not stated
- Inclusion of all randomized participants: not stated

**Participants**
- Number of participants: 58 randomized
- Inclusion criteria: male children aged 2 to 10 years; stool positive for Vibrio cholerae; acute watery diarrhea < 24 h duration; signs of severe dehydration (sunken eyes, very dry mouth and tongue, absence of tears, loss of skin elasticity, diminished urine output)
- Exclusion criteria: antibiotic use; received intravenous fluid; systemic illness

**Interventions**
1. Reduced osmolarity (glucose-based)ORS
2. Reduced osmolarity (rice-based)ORS
3. Standard ORS

See Appendix 2 for the ORS compositions
Co-interventions: tetracycline tablet (50 mg/kg/day of body weight in 4 divided doses for 3 days after correction of initial dehydration)

**Outcomes**
1. Incidence of symptomatic hyponatremia
2. Total stool output (L)
3. Total ORS intake (L)
4. Body weight (kg)
5. Serum sodium level (mmol/L)
6. Serum sodium level < 125 mmol/L
7. Serum sodium level 125 to 130 mmol/L
8. Duration of diarrhea

**Notes**
- Location: Infectious Diseases Hospital, Calcutta, India
- Date: August 1995 to May 1998

**Faruque 1996**

**Methods**
- Generation of allocation sequence: block randomization (adequate)
- Concealment of allocation: randomization incorporated into serially numbered boxes of ORS packets
- Blinding: not stated
- Inclusion of all randomized participants: not stated

**Participants**
- Inclusion criteria: males aged 15 to 49 presenting severe cholera-like diarrhea of < 24 h duration; severe dehydration requiring intravenous therapy (patients with clinical signs of dehydration who had postural hypotension with a feeble or imperceptible radial pulse and systolic blood pressure of less than 90 mmHg); dark-field positive for Vibrio cholerae
- Exclusion criteria: no concurrent illness or recognized chronic disease; recent history of antibiotic use

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Reduced osmolarity oral rehydration solution for treating cholera (Review)  
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Faruque 1996 (Continued)

| Interventions | 1. Reduced osmolarity (glucose-based)ORS  
2. Standard ORS  
See Appendix 2 for the ORS compositions  
Co-interventions: intravenous therapy to correct dehydration over a period of 3 to 4 h; saline solution (Na 133; Cl 98; K 13; acetate 48 mmol/L); erythromycin (500 mg, 6 hourly); additional intravenous therapy (rapidly administered) for patients who went into negative fluid balance and clinical signs of dehydration reappeared (saline solution consisting of Na 133; Cl 98; K 13; acetate 48 mmol/L) |
|---|---|
| Outcomes | 1. Need for unscheduled intravenous infusion<sup>a</sup>  
2. Stool volume in first 24 h after admission/randomization (ml/kg)<sup>a</sup>  
3. Duration of diarrhea (h)<sup>a</sup>  
4. Vomiting during rehydration (0 to 24 h and 24 to 48 h)<sup>a</sup>  
5. Stool output (ml/kg) 24 to 48 h  
6. Stool output (ml/kg) 0 to 48 h  
7. ORS intake (ml/kg) 0 to 24 h  
8. ORS intake (ml/kg) 24 to 48 h  
9. ORS intake (ml/kg) 0 to 48 h  
10. Urine output (ml/kg) 0 to 24 h  
11. Urine output (ml/kg) 24 to 48 h  
12. Urine output (ml/kg) 0 to 48 h  
13. Serum sodium (mmol/L) 24 h and 48 h  
14. Serum potassium (mmol/L) at 24 h and 48 h  
15. Serum chloride (mmol/L) at 24 h and 48 h  
16. Serum total carbon dioxide at 24 h and 48 h  
17. Number of patients with a 24-h serum sodium of < 125 mmol/L, 125 to 130 mmol/L, and > 130 mmol/L<sup>a</sup> |
| Notes | Location: International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)  
Date: second half of 1994 |

### Punjabi 1995

| Methods | Generation of allocation sequence: not stated  
Concealment of allocation: not stated  
Blinding: patient and provider blinded  
Inclusion of all randomized participants: not stated |
|---|---|
| Participants | Number of participants: 160 randomized  
Inclusion criteria: adult cholera patients with severe dehydration  
Exclusion criteria: not stated |
| Interventions | Reduced osmolarity (glucose-based)ORS  
Standard ORS  
See Appendix 2 for the ORS compositions |
| Outcomes | 1. Need for unscheduled intravenous infusion (%)<sup>a</sup>  
2. Stool volume in first 24 h after admission/randomization (ml)<sup>a</sup>  
3. Duration of diarrhea (h)<sup>a</sup>  
4. Vomiting during rehydration (total ml) |

---

<sup>a</sup> Outcome measures.
Punjabi 1995  *(Continued)*

| 5. Mean absolute volume of stool output  |
| 6. Stool output as bodyweight (ml/kg)  |
| 7. Mean volume of vomiting (ml) 24 h after randomization  |
| 8. Mean duration of vomiting (h)  |
| 9. Number of treatment failures  |

**Notes**

Location: Prf. Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia
Date: January 1994 to January 1995

Cl: chloride; K: potassium; Na: sodium; ORS: oral rehydration solution.

*Outcomes assessed in this review.*

**Characteristics of excluded studies  [ordered by study ID]**

| Bhan 1995 | Participants did not have cholera.  |
| Dutta 2001 | Included participants with cholera and non-cholera diarrhea. Results reported in aggregate; we have requested the disaggregated data.  |
| Gutman 1969 | Participants were not administered standard or reduced osmolarity ORS.  |
| Mahalanabis 1974 | Participants were not administered standard or reduced osmolarity ORS.  |
| Nalin 1968 | Non-randomized trial. Participants were not administered reduced osmolarity ORS.  |

ORS: oral rehydration solution

**Characteristics of ongoing studies  [ordered by study ID]**

**Bangladesh**

| Trial name or title | To investigate further the impact of the low osmolarity ORS on the incidence and prevalence of hyponatremia in diarrheic patients, especially those with cholera.  |
| Methods | -  |
| Participants | Not known.  |
### Bangladesh (Continued)

| Interventions          | 1. Reduced osmolarity ORS.  
<table>
<thead>
<tr>
<th></th>
<th>2. Standard ORS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Not known.</td>
</tr>
<tr>
<td>Starting date</td>
<td>Not known.</td>
</tr>
<tr>
<td>Contact information</td>
<td>Centre for Health and Population Research, (ICDDR,B).</td>
</tr>
</tbody>
</table>
| Notes                  | Location: Dhaka, Bangladesh.  
|                        | Awaiting details.            |

### India

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Phase IV controlled trial to investigate further the impact of the low osmolarity ORS on the incidence and prevalence of hyponatremia in diarrheic patients, especially those with cholera.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>-</td>
</tr>
<tr>
<td>Participants</td>
<td>About 20,000 patients (adults and children) with diarrhea (non-cholera and cholera).</td>
</tr>
</tbody>
</table>
| Interventions          | 1. Reduced osmolarity ORS.  
|                        | 2. Standard ORS.            |
| Outcomes               | Not known.                                                                  |
| Starting date          | Not known.                                                                 |
| Contact information    | Awaiting details.                                                              |
| Notes                  | Location: Calcutta, India.                                                   
|                        | Awaiting details.                                                              |

ORS: oral rehydration solution
## Data and analyses

### Comparison 1. Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Need for unscheduled intravenous infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 Children</td>
<td>2</td>
<td>93</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.57 [0.29, 1.11]</td>
</tr>
<tr>
<td>1.2 Adults</td>
<td>3</td>
<td>523</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.93 [0.70, 1.24]</td>
</tr>
<tr>
<td>2 Biochemical hyponatremia (serum sodium &lt; 130 mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 Children</td>
<td>1</td>
<td>39</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.58 [0.53, 4.74]</td>
</tr>
<tr>
<td>2.2 Adults</td>
<td>3</td>
<td>426</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.69 [1.06, 2.69]</td>
</tr>
<tr>
<td>3 Severe biochemical hyponatremia (serum sodium &lt; 125 mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Children</td>
<td>1</td>
<td>39</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.58 [0.62, 4.04]</td>
</tr>
<tr>
<td>3.2 Adults</td>
<td>3</td>
<td>426</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.69 [1.06, 2.69]</td>
</tr>
<tr>
<td>4 Duration of diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 Children</td>
<td>3</td>
<td>132</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.08 [-4.58, 2.41]</td>
</tr>
<tr>
<td>4.2 Adults</td>
<td>4</td>
<td>586</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.42 [0.29, 2.55]</td>
</tr>
<tr>
<td>5 Stool volume in first 24 hours after admission or randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1 Children</td>
<td>1</td>
<td>58</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.13 [-0.43, 0.17]</td>
</tr>
<tr>
<td>5.2 Adults</td>
<td>3</td>
<td>523</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.13 [-0.43, 0.17]</td>
</tr>
<tr>
<td>6 Vomiting during rehydration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1 Children</td>
<td>0</td>
<td>0</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>6.2 Adults</td>
<td>2</td>
<td>363</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.14 [0.92, 1.40]</td>
</tr>
</tbody>
</table>

### Comparison 2. Reduced osmolarity (rice-based) oral rehydration solution (ORS) versus standard ORS

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Biochemical hyponatremia (serum sodium &lt; 130 mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 Children</td>
<td>1</td>
<td>39</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.05 [0.31, 3.62]</td>
</tr>
<tr>
<td>1.2 Adults</td>
<td>1</td>
<td>63</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.36 [0.08, 1.74]</td>
</tr>
<tr>
<td>2 Severe biochemical hyponatremia (serum sodium &lt; 125 mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 Children</td>
<td>1</td>
<td>39</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.35 [0.02, 8.10]</td>
</tr>
<tr>
<td>2.2 Adults</td>
<td>1</td>
<td>63</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>3 Duration of diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Children</td>
<td>1</td>
<td>39</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-16.85 [-21.22, -12.48]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS, Outcome 1 Need for unscheduled intravenous infusion.

**Review:** Reduced osmolarity oral rehydration solution for treating cholera  
**Comparison:** 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS  
**Outcome:** 1 Need for unscheduled intravenous infusion

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS n/N</th>
<th>Standard ORS n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alam 2000</td>
<td>0/19</td>
<td>3/16</td>
<td></td>
<td>4.3 %</td>
<td>0.12 [ 0.01, 2.19 ]</td>
</tr>
<tr>
<td>Choice 2001</td>
<td>8/26</td>
<td>14/32</td>
<td></td>
<td>14.3 %</td>
<td>0.70 [ 0.35, 1.41 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>45</strong></td>
<td><strong>48</strong></td>
<td></td>
<td><strong>18.7 %</strong></td>
<td><strong>0.57 [ 0.29, 1.11 ]</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>8 (Reduced osmol. ORS), 17 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 1.45, df = 1 (P = 0.23); I² = 31%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 1.65 (P = 0.099)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alam 1999</td>
<td>45/147</td>
<td>43/153</td>
<td></td>
<td>48.2 %</td>
<td>1.09 [ 0.77, 1.55 ]</td>
</tr>
<tr>
<td>Faruque 1996</td>
<td>4/34</td>
<td>7/29</td>
<td></td>
<td>8.6 %</td>
<td>0.49 [ 0.16, 1.50 ]</td>
</tr>
<tr>
<td>Punjabi 1995</td>
<td>16/78</td>
<td>22/82</td>
<td></td>
<td>24.5 %</td>
<td>0.76 [ 0.43, 1.34 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>259</strong></td>
<td><strong>264</strong></td>
<td></td>
<td><strong>81.3 %</strong></td>
<td><strong>0.93 [ 0.70, 1.24 ]</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>65 (Reduced osmol. ORS), 72 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 2.51, df = 2 (P = 0.28); I² = 20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 0.51 (P = 0.61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>304</strong></td>
<td><strong>312</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.86 [ 0.66, 1.12 ]</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>73 (Reduced osmol. ORS), 89 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 4.94, df = 4 (P = 0.29); I² = 19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 1.12 (P = 0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Analysis 1.2. Comparison 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS, Outcome 2 Biochemical hyponatremia (serum sodium < 130 mmol/L).

Review: Reduced osmolarity oral rehydration solution for treating cholera
Comparison: 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS
Outcome: 2 Biochemical hyponatremia (serum sodium < 130 mmol/L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS n/N</th>
<th>Standard ORS n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutta 2000</td>
<td>6/19</td>
<td>4/20</td>
<td>13.9 %</td>
<td>1.58</td>
<td>[0.53, 4.74]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>19</td>
<td>20</td>
<td></td>
<td>13.9 %</td>
<td>1.58 [0.53, 4.74]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alam 1999</td>
<td>29/147</td>
<td>16/153</td>
<td>55.9 %</td>
<td>1.89</td>
<td>[1.07, 3.33]</td>
</tr>
<tr>
<td>Bhattacharya 1998</td>
<td>5/33</td>
<td>5/30</td>
<td>18.7 %</td>
<td>0.91</td>
<td>[0.29, 2.83]</td>
</tr>
<tr>
<td>Faruque 1996</td>
<td>7/34</td>
<td>3/29</td>
<td>11.5 %</td>
<td>1.99</td>
<td>[0.57, 7.01]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>214</td>
<td>212</td>
<td></td>
<td>86.1 %</td>
<td>1.69 [1.06, 2.69]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>233</td>
<td>232</td>
<td></td>
<td>100.0 %</td>
<td>1.67 [1.09, 2.57]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.82 (P = 0.42)

Heterogeneity: Chi² = 1.35, df = 2 (P = 0.51); I² = 0.0%
Test for overall effect: Z = 2.20 (P = 0.028)

Heterogeneity: Chi² = 1.36, df = 3 (P = 0.71); I² = 0.0%
Test for overall effect: Z = 2.35 (P = 0.019)
Analysis 1.3. Comparison 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS, Outcome 3 Severe biochemical hyponatremia (serum sodium < 125 mmol/L).

Review: Reduced osmolarity oral rehydration solution for treating cholera
Comparison: 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS
Outcome: 3 Severe biochemical hyponatremia (serum sodium < 125 mmol/L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Children</td>
<td>0/19</td>
<td>1/20</td>
<td>0.35 [ 0.02, 8.10 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>19</td>
<td>20</td>
<td>0.35 [ 0.02, 8.10 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alam 1999</td>
<td>7/147</td>
<td>5/153</td>
<td>1.46 [ 0.47, 4.49 ]</td>
<td></td>
</tr>
<tr>
<td>Bhattacharya 1998</td>
<td>0/33</td>
<td>0/30</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td>Faruque 1996</td>
<td>3/34</td>
<td>0/29</td>
<td>6.00 [ 0.32, 111.56 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>214</td>
<td>212</td>
<td>1.91 [ 0.68, 5.31 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>214</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>233</td>
<td>232</td>
<td>1.58 [ 0.62, 4.04 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>233</td>
<td>232</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.65 (P = 0.51)

Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.22)

Heterogeneity: Chi² = 1.70, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
### Analysis 1.4. Comparison 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS, Outcome 4 Duration of diarrhea.

**Review:** Reduced osmolarity oral rehydration solution for treating cholera

**Comparison:** 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS

**Outcome:** 4 Duration of diarrhea

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>1 Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alam 2000</td>
<td>19</td>
<td>21.44 (1.32)</td>
<td>16</td>
<td>19.97 (1.99)</td>
<td>24.7 %</td>
</tr>
<tr>
<td>Choice 2001</td>
<td>26</td>
<td>82.9 (27.5)</td>
<td>32</td>
<td>78.6 (24.5)</td>
<td>5.3 %</td>
</tr>
<tr>
<td>Dutta 2000</td>
<td>19</td>
<td>33.89 (16.4)</td>
<td>20</td>
<td>38.47 (17.4)</td>
<td>7.6 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>64</td>
<td></td>
<td>68</td>
<td></td>
<td>37.6 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0; Chi² = 1.41, df = 2 (P = 0.49); I² = 0.0%
Test for overall effect: Z = 2.46 (P = 0.014)

<table>
<thead>
<tr>
<th></th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alam 1999</td>
<td>147</td>
<td>46 (18.2)</td>
<td>153</td>
<td>43 (18.6)</td>
<td>18.6 %</td>
</tr>
<tr>
<td>Bhattacharya 1998</td>
<td>33</td>
<td>37.2 (9.9)</td>
<td>30</td>
<td>46.9 (11.9)</td>
<td>15.7 %</td>
</tr>
<tr>
<td>Faruque 1996</td>
<td>34</td>
<td>49.9 (18.7)</td>
<td>29</td>
<td>57.1 (17.9)</td>
<td>9.4 %</td>
</tr>
<tr>
<td>Punjabi 1995</td>
<td>82</td>
<td>44.4 (13.3)</td>
<td>78</td>
<td>42.7 (13.5)</td>
<td>18.7 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>296</td>
<td></td>
<td>290</td>
<td></td>
<td>62.4 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 32.00; Chi² = 16.80, df = 3 (P = 0.00078); I² = 82%
Test for overall effect: Z = 0.80 (P = 0.43)

<table>
<thead>
<tr>
<th></th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>360</td>
<td></td>
<td>358</td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 12.55; Chi² = 20.97, df = 6 (P = 0.002); I² = 71%
Test for overall effect: Z = 0.61 (P = 0.54)
### Analysis 1.5. Comparison 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS, Outcome 5 Stool volume in first 24 hours after admission or randomization.

**Review:** Reduced osmolarity oral rehydration solution for treating cholera

**Comparison:** 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS

**Outcome:** 5 Stool volume in first 24 hours after admission or randomization

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Random</td>
</tr>
<tr>
<td>1 Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choice 2001</td>
<td>26</td>
<td>203.7 (100.6)</td>
<td>32</td>
<td>201 (82)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>26</strong></td>
<td><strong>32</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alam 1999</td>
<td>147</td>
<td>212 (97)</td>
<td>153</td>
<td>207 (90)</td>
<td></td>
</tr>
<tr>
<td>Faruque 1996</td>
<td>34</td>
<td>205.6 (109)</td>
<td>29</td>
<td>287.5 (103.5)</td>
<td></td>
</tr>
<tr>
<td>Punjabi 1995</td>
<td>78</td>
<td>3792 (2844)</td>
<td>82</td>
<td>3894 (2190)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>259</strong></td>
<td><strong>264</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** not applicable

**Test for overall effect:** $Z = 0.11$ (P = 0.91)

| Total (95% CI) | 285 | 296 | 100.0 % | -0.13 | [ -0.43, 0.17 ] |

**Heterogeneity:** $\tau^2 = 0.06$; $\chi^2 = 8.21$, df = 3 (P = 0.04); $I^2$ =63%

**Test for overall effect:** $Z = 0.85$ (P = 0.39)
### Analysis 1.6. Comparison 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS, Outcome 6 Vomiting during rehydration.

**Review:** Reduced osmolarity oral rehydration solution for treating cholera

**Comparison:** 1 Reduced osmolarity (glucose-based) oral rehydration solution (ORS) versus standard ORS

**Outcome:** 6 Vomiting during rehydration

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS n/N</th>
<th>Standard ORS n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>0/0</td>
<td>0/0</td>
<td>0.0 %</td>
<td>0.0 [0.0, 0.0]</td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>2 Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Alam 1999</td>
<td>74/147</td>
<td>64/153</td>
<td>75.4 %</td>
<td>1.20 [0.94, 1.54]</td>
<td>0.94 [0.65, 1.37]</td>
</tr>
<tr>
<td>Faruque 1996</td>
<td>21/34</td>
<td>19/29</td>
<td>24.6 %</td>
<td>0.94 [0.65, 1.37]</td>
<td>0.94 [0.65, 1.37]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>181 182</td>
<td></td>
<td>100.0 %</td>
<td>1.14 [0.92, 1.40]</td>
<td>1.20 [0.94, 1.54]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi^2 = 1.18, df = 1 (P = 0.28); I^2 = 15%
Test for overall effect: Z = 1.23 (P = 0.22)
### Analysis 2.1. Comparison 2 Reduced osmolarity (rice-based) oral rehydration solution (ORS) versus standard ORS, Outcome 1 Biochemical hyponatremia (serum sodium < 130 mmol/L).

Review: Reduced osmolarity oral rehydration solution for treating cholera

Comparison: 2 Reduced osmolarity (rice-based) oral rehydration solution (ORS) versus standard ORS

Outcome: 1 Biochemical hyponatremia (serum sodium < 130 mmol/L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutta 2000</td>
<td>4/19</td>
<td>4/20</td>
<td></td>
<td>42.7 %</td>
<td>1.05 [ 0.31, 3.62 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>19</strong></td>
<td><strong>20</strong></td>
<td></td>
<td></td>
<td><strong>42.7 %</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>4 (Reduced osmol. ORS), 4 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 0.08 (P = 0.94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhattacharya 1998</td>
<td>2/33</td>
<td>5/30</td>
<td></td>
<td>57.3 %</td>
<td>0.36 [ 0.08, 1.74 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>33</strong></td>
<td><strong>30</strong></td>
<td></td>
<td></td>
<td><strong>57.3 %</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>2 (Reduced osmol. ORS), 5 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 1.27 (P = 0.20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>52</strong></td>
<td><strong>50</strong></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>6 (Reduced osmol. ORS), 9 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.11, df = 1 (P = 0.29); I^2 = 10%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 0.87 (P = 0.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Favours reduced ORS**
- **Favours standard ORS**
### Analysis 2.2. Comparison 2 Reduced osmolarity (rice-based) oral rehydration solution (ORS) versus standard ORS, Outcome 2 Severe biochemical hyponatremia (serum sodium < 125 mmol/L).

**Review**: Reduced osmolarity oral rehydration solution for treating cholera

**Comparison**: Reduced osmolarity (rice-based) oral rehydration solution (ORS) versus standard ORS

**Outcome**: Severe biochemical hyponatremia (serum sodium < 125 mmol/L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td><strong>1 Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutta 2000</td>
<td>0/19</td>
<td>1/20</td>
<td>0.35 [ 0.02, 8.10 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>19</td>
<td>20</td>
<td>0.35 [ 0.02, 8.10 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong>:</td>
<td>0 (Reduced osmol. ORS), 1 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong>:</td>
<td>not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong>:</td>
<td>Z = 0.65 (P = 0.51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2 Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhattacharya 1998</td>
<td>0/33</td>
<td>0/30</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>33</td>
<td>30</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong>:</td>
<td>0 (Reduced osmol. ORS), 0 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong>:</td>
<td>not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong>:</td>
<td>Z = 0.0 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>52</td>
<td>50</td>
<td>0.35 [ 0.02, 8.10 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong>:</td>
<td>0 (Reduced osmol. ORS), 1 (Standard ORS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong>:</td>
<td>Chi² = 0.00, df = 0 (P=0.00001); I² =100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong>:</td>
<td>Z = 0.65 (P = 0.51)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Reduced osmolarity oral rehydration solution for treating cholera (Review)  
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Analysis 2.3. Comparison 2 Reduced osmolarity (rice-based) oral rehydration solution (ORS) versus standard ORS, Outcome 3 Duration of diarrhea.

Review: Reduced osmolarity oral rehydration solution for treating cholera

Comparison: 2 Reduced osmolarity (rice-based) oral rehydration solution (ORS) versus standard ORS

Outcome: 3 Duration of diarrhea

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Reduced osmol. ORS</th>
<th>Standard ORS</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>1 Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutta 2000</td>
<td>19 29.34 (21)</td>
<td>20 38.47 (17.4)</td>
<td>12.9 %</td>
<td>-9.13</td>
<td>[-21.27, 3.01]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>19</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.9 %</td>
<td>-9.13</td>
<td>[-21.27, 3.01]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.47 (P = 0.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 Adults

| Bhattacharya 1998 | 33 28.9 (5.7) | 30 46.9 (11.9) | 87.1 % | -18.00 | [-22.68, -13.32] |
| Subtotal (95% CI) | 33                | 30            |                 |        |                |
|                   | 87.1 %            | -18.00        | [-22.68, -13.32] |        |                |
|                   | Heterogeneity: not applicable |
| Test for overall effect: Z = 7.54 (P < 0.00001) |

Total (95% CI)

|                   | 52                | 50            | 100.0 %       | -16.85 | [-21.22, -12.48] |
|                   | Heterogeneity: Ch2 = 1.79, df = 1 (P = 0.18); I² = 44% |
| Test for overall effect: Z = 7.56 (P < 0.00001) |
| Test for subgroup differences: Ch2 = 1.79, df = 1 (P = 0.18); I² = 44% |

APPROACHES

Appendix 1. Search methods: detailed search strategies

<table>
<thead>
<tr>
<th>Search set</th>
<th>CIDG SRb</th>
<th>CENTRALb</th>
<th>MEDLINEb</th>
<th>EMBASEb</th>
<th>LILACSB</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>cholera</td>
<td>cholera</td>
<td>CHOLERA</td>
<td>CHOLERA</td>
<td>cholera</td>
</tr>
<tr>
<td>2</td>
<td>rehydration solutions</td>
<td>oral rehydration solution</td>
<td>cholera</td>
<td>cholera</td>
<td>oral rehydration</td>
</tr>
<tr>
<td>3</td>
<td>fluid therapy</td>
<td>fluid therapy</td>
<td>1 or 2</td>
<td>1 or 2</td>
<td>hypotonic</td>
</tr>
<tr>
<td>4</td>
<td>hypotonic</td>
<td>hypotonic solution</td>
<td>REHYDRATION SOLUTIONS</td>
<td>FLUID THERAPY</td>
<td>reduced osmolarity</td>
</tr>
</tbody>
</table>

Reduced osmolarity oral rehydration solution for treating cholera (Review)

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Continued

<table>
<thead>
<tr>
<th>5</th>
<th>ORS</th>
<th>ORS</th>
<th>FLUID THERAPY</th>
<th>HYPOTONIC SOLUTION</th>
<th>2 or 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-</td>
<td>2 or 3 or 4 or 5</td>
<td>HYPOTONIC SOLUTIONS</td>
<td>ORAL REHYDRATION THERAPY</td>
<td>1 and 5</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>1 and 6</td>
<td>OSMOLAR CONCENTRATION</td>
<td>ORAL REHYDRATION SOLUTION</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>oral rehydration solution</td>
<td>oral rehydration solution</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>ORS</td>
<td>ORS</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>osmolar$^a$</td>
<td>OSMOLARITY</td>
<td>-</td>
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<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>osmolality</td>
<td>HYPEROSMOLARITY</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>-</td>
<td>reduced osmolarity</td>
<td>osmolar$^b$</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
<td>hypo-osmolar</td>
<td>osmolality</td>
<td>-</td>
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<tr>
<td>14</td>
<td>-</td>
<td>-</td>
<td>4-13/OR</td>
<td>reduced ADJ osmolarity</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>-</td>
<td>3 and 14</td>
<td>Hypo ADJ osmolar$^b$</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>-</td>
<td>Limit 15 to human</td>
<td>4-15/OR</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 and 16</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Limit 17 to human</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Cochrane Infectious Diseases Group Specialized Register.

$^b$Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Alderson 2004); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 2. Composition of oral rehydration solutions used in the trials

<table>
<thead>
<tr>
<th>Oral rehydration solution type</th>
<th>Trials</th>
<th>Sodium (mmol/L)</th>
<th>Potassium (mmol/L)</th>
<th>Chloride (mmol/L)</th>
<th>Citrate (mmol/L)</th>
<th>Glucose (mmol/L)</th>
<th>Rice powder (g)</th>
<th>Total osmolarity (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>All trials</td>
<td>90</td>
<td>20</td>
<td>80</td>
<td>10</td>
<td>111</td>
<td>-</td>
<td>311</td>
</tr>
</tbody>
</table>

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(Continued)

<table>
<thead>
<tr>
<th>Reduced osmolarity (glucose-based)</th>
<th>Dutta 2001</th>
<th>60</th>
<th>20</th>
<th>50</th>
<th>10</th>
<th>84</th>
<th>-</th>
<th>224</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faruque 1996</td>
<td>67</td>
<td>20</td>
<td>66</td>
<td>7</td>
<td>89</td>
<td>-</td>
<td>249</td>
</tr>
<tr>
<td></td>
<td>Bhat-tacharya 1998, Dutta 2000</td>
<td>70</td>
<td>20</td>
<td>80</td>
<td>8</td>
<td>90</td>
<td>-</td>
<td>268</td>
</tr>
<tr>
<td></td>
<td>Alam 1999, Choice 2001</td>
<td>75</td>
<td>20</td>
<td>65</td>
<td>10</td>
<td>75</td>
<td>-</td>
<td>245</td>
</tr>
</tbody>
</table>

| Reduced osmolarity (rice-based)  | Bhat-tacharya 1998, Dutta 2000 | 70  | 20  | 80  | 8   | -   | 50  | 178 |

**WHAT'S NEW**

Last assessed as up-to-date: 30 October 2005.

20 October 2008 | Amended | Converted to new review format with minor editing.

**HISTORY**


Review first published: Issue 4, 2004

31 October 2005 | New search has been performed | New studies sought but none found.

12 January 2005 | Amended | Issue 2, 2005: Simplified graph format (no changes to the results) and updated references.
CONTRIBUTIONS OF AUTHORS

Colleen Murphy (CM) initiated the review and is the guarantor. CM developed the eligibility and data extraction forms with Seokyung Hahn (SH) and Jimmy Volmink (JV) providing input. CM and JV selected the trials for inclusion in the review. CM and SH extracted the data and assessed trial quality, and CM contacted authors for additional information. CM entered the data and conducted the analysis. CM wrote the first draft of the review with all reviewers contributing to the final text and analysis.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Global Health Council, USA.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2004, Issue 4 (first review version): We have added “Biochemical hyponatremia as defined by trialists” as a secondary outcome measure because it provides an important measure of potential risk for people with cholera.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholera [*complications]; Diarrhea [*therapy]; Hyponatremia [etiology]; Osmolar Concentration; Randomized Controlled Trials as Topic; Rehydration Solutions [adverse effects; chemistry; *therapeutic use]

MeSH check words

Adult; Child; Humans