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Abstract

Objectives To compare reduced osmolarity oral rehydration solution with standard World Health Organization oral rehydration solution in children with acute diarrhoea.

Design Systematic review of randomised controlled trials.

Studies 15 randomised controlled trials including 2397 randomised patients.

Outcomes The primary outcome was unscheduled intravenous infusion; secondary outcomes were stool output, vomiting, and hyponaetraemia.

Results In a meta-analysis of nine trials for the primary outcome, reduced osmolarity rehydration solution was associated with fewer unscheduled intravenous infusions compared with standard WHO rehydration solution (odds ratio 0.61, 95% confidence interval 0.47 to 0.81). Three trials reported that no patients required unscheduled intravenous infusion. Trials reporting secondary outcomes suggested that in the reduced osmolarity rehydration solution group, stool output was lower (standardised mean difference in the log scale −0.214 (95% confidence interval −0.305 to −0.123; 13 trials) and vomiting was less frequent (odds ratio 0.71, 0.55 to 0.92; six trials). Six trials sought presence of hyponaetraemia, with events in three studies, but no significant difference between the two arms.

Conclusion In children admitted to hospital with dehydration associated with diarrhoea, reduced osmolarity rehydration solution is associated with reduced need for unscheduled intravenous infusions, lower stool volume, and less vomiting compared with standard WHO rehydration solution.

Introduction

Diarrhoea remains a leading cause of childhood death in developing countries. The main complication is dehydration, which until the early 1960s was treated with intravenous infusion. Solutions of oral rehydration salts are now the main treatment and are particularly useful when intravenous fluids are in short supply, health services are basic, and there is a shortage of skilled staff.1 The combination of salt and sugar probably enhances absorption of fluid because sodium and glucose transport in the small intestine are coupled; glucose promotes absorption of both sodium ions and water.2 Oral rehydration solutions have proved both safe and effective worldwide in hospital settings and are now widely used in the home to prevent dehydration.3 4

For more than two decades, the World Health Organization has recommended a standard formulation of glucose based oral rehydration solution with 90 mmol/l of sodium and 110 mmol/l of glucose and a total osmolarity of 311 mmol/l. It remains unclear however, whether this is the optimum sodium concentration. Some studies have found patients with blood sodium concentrations above the normal level of 150 mmol/l.5 6 7 Laboratory work suggests that lower concentrations of sodium and glucose enhance solute induced water absorption.6 7

We conducted a systematic review of all relevant randomised controlled trials comparing the effects of reduced osmolarity and standard WHO oral rehydration solutions. We confined the review to children, as they are most vulnerable to dehydration and electrolyte imbalance from diarrhoea.

Methods

Study inclusion and characteristics

We included only randomised controlled trials, defined as a trial in which the subjects were assigned prospectively to one of two or more interventions by random allocation. This excludes quasirandomised designs. Patients included were children with acute diarrhoea for less than 5 days who were treated either by reduced
The primary outcome was specified as the need for unscheduled intravenous infusion during the course of treatment. This was defined as clinical requirement for intravenous infusion after oral rehydration had been started. We chose unscheduled intravenous infusion as the primary outcome because it is a pragmatic outcome that is relevant to health providers and represents failed oral treatment. Other outcomes were stool output, vomiting during rehydration, and presence of hyponatraemia (serum sodium concentration <150 mmol/l) during follow up.

**Search strategy**

We searched the following databases for published clinical trials: Medline (1966 to June 2001); Embase (1988 to May 2001); Cochrane controlled trials register in the Cochrane Library (Issue 2, 2001); and Current Contents (June 2001). We used child, diarrhoea, fluid therapy, oral rehydration, osmolar, and rehydration solutions as search terms. We also checked the citations of existing reviews and trial reports. For unpublished data and ongoing trials, we contacted current researchers and key agencies, including the WHO, the Centers for Disease Control, Atlanta, and the International Centre for Diarrhoeal Disease Research, Bangladesh.

**Data extraction and synthesis**

We used the standard methods of the Cochrane infectious diseases group to prepare the protocol, apply inclusion criteria, assess quality, and extract data. We assessed quality by adequacy of concealment of allocation, generation of allocation sequence, blinding, and follow up of patients. The first two authors independently extracted data on relevant outcome measures using a standardised data abstraction form, and any disagreements were resolved by discussion.

We used the Mantel-Haenszel odds ratio for binary outcomes. The odds ratios were not estimated when neither intervention group found any event. We used the standardised mean difference for continuous outcomes. We combined studies using a fixed effect method based on a weighted average of the results with weights proportional to the inverse of the variance. For all estimates, we calculated 95% confidence intervals. We tested statistical heterogeneity using $\chi^2$ tests, with a P value $<0.1$ indicating significance. We had prespecified potential sources of heterogeneity for analysis. We examined publication bias using a funnel plot and a regression approach to assess asymmetry of the plot. We also did a sensitivity analysis to assess the effect of adequacy of concealment of allocation.

**Results**

**Profile of studies**

Of 41 identified studies, six were not randomised trials, eight had not used glucose based reduced osmolarity rehydration solution, six had not used standard WHO rehydration solution, two were in adults, and two did not report on any of the relevant outcomes. Seventeen studies in 16 published reports met the inclusion criteria. One paper reported on two trials, one in the United States and one in Panama, and we present these as separate studies. We contacted the authors of three papers, as we judged these were three reports of the same trial. As we have not received a response, we included only the paper with the largest number of patients.

**Description and quality of studies**

Details of the 13 trials included in the analysis and their patient characteristics are available on the BMJ's website. Included studies were from Egypt (three studies), Bangladesh (three), Mexico (one), Colombia (one), India (three), Panama (one), and the United States (one). Two other studies were multicentre trials; one was conducted in Brazil, India, Mexico, and Peru and the other in Bangladesh, Brazil, India, Peru, and Vietnam.

Three trials included children with cholera. Children were aged 1-36 months in all trials except one, which included children up to 5 years old. All children had some degree of clinical dehydration. One trial treated all children on day 1 with intravenous infusion, and those with a stool output of 80 ml/kg/24 h were then randomised. Five trials included children with severe dehydration. Five trials included malnourished children. The number of breastfed children was reported in eight trials. Fully weaned children were included in one trial.

We deviated slightly from the osmolarity definitions in our refereed protocol published in the Cochrane Library. We defined reduced osmolarity as $<250$ mmol/l, but some studies defined reduced osmolarity as higher than this, and we therefore extended our limit to $<270$ mmol/l. We also included two studies that used a WHO oral rehydration solution with a total osmolarity of 331 mmol/l rather than 311 mmol/l but with the same sodium and glucose combination. All but three trials used a glucose based reduced osmolarity rehydration solution; one used sucrose, another maltodextrin, and the third used L-alanine with glucose.

Nine trials reported methods that assured adequate concealment of allocation. Seven studies stated they were double blinded, and eight did not mention blinding.

**Quantitative data synthesis**

Figures 1-4 show the meta-analyses for the four outcomes. Information on the primary outcome
(unscheduled intravenous infusion) was available in 12 trials (n = 2085), but in three of these patients no evidence was provided in either group required infusion. In the meta-analysis of nine trials, the need for intravenous infusion was significantly reduced for participants who received reduced osmolality rehydration solution compared with those receiving WHO rehydration solution (odds ratio 0.61, 95% confidence interval 0.47 to 0.81).

Thirteen trials reported stool output during rehydration. These trials measured stool output in various ways using different units. We therefore used the standardised mean difference to analyse these data. Since the stool output in diarrhoeal disease showed a positive skewed distribution with clinical improvement, we used a log-normal approximation. The pooled standardised mean difference in the log scale is −0.214 (95% confidence interval −0.305 to −0.123), which suggests that the reduced osmolality rehydration solution resulted in significantly less stool output than the WHO solution. Data from one trial was not combined with the others in the meta-analysis because this trial measured stool output for much longer than the others (see BMJ website for details of results).

Six trials reported on vomiting during rehydration. The tendency was for fewer patients to vomit in the reduced osmolality rehydration solution group (odds ratio 0.71, 95% confidence interval 0.55 to 0.92).

Six trials reported on hyponatraemia. In three of these six trials, no patients had hyponatraemia. The meta-analysis of the three trials in which participants developed hyponatraemia showed no significant difference between the groups (odds ratio 1.45, 95% confidence interval 0.93 to 2.26). We found no evidence of statistical heterogeneity of treatment effect for any of the four outcomes.

The funnel plot of the primary outcome showed no significant evidence of publication bias (fig 5). The regression method used to assess funnel plot asymmetry gave an intercept of −0.72 with a P value of 0.29. A sensitivity analysis restricted to studies with clear evidence of adequate concealment of allocation produced results that did not differ greatly from those of the full meta-analysis. For example, the pooled odds ratios of the seven trials for the primary outcome with adequate concealment of allocation was 0.61 (0.46 to 0.82).

**Discussion**

We found that reduced osmolality rehydration solution was more effective than standard WHO rehydration solution in first line treatment of children with diarrhoea. It reduced the need for unscheduled intravenous infusion, stool output during rehydration, and the number of patients with vomiting during oral rehydration treatment. The reduced osmolality rehydration solution did not seem to increase the risk of developing hyponatraemia compared with the standard WHO solution, although we cannot exclude this possibility.

We examined trials of oral rehydration salts in children admitted to hospital with dehydration because of diarrhoea. The trials do not provide any direct evidence for or against use of oral rehydration solutions at home to prevent dehydration; nor do they provide any direct evidence that reduced osmolality solutions are more effective in preventing dehydration in the home. Oral rehydration solutions are widely used to prevent dehydration, and further research is therefore needed in this area.

**Choice of primary outcome**

We stand by our selection of unscheduled intravenous infusion rather than volume of diarrhoea as the primary outcome. Some specialists consider that volume of diarrhoea is more appropriate, probably because it reflects the animal and human perfusion experiments that provide part of the rationale for a reduced osmolality rehydration solution. Unscheduled intravenous infusion is pragmatic; it provides a measure of failed oral rehydration and has implica-
tions for healthcare resources. For these reasons, we
preserved this as the primary outcome.

When we reviewed the studies for inclusion, most
trials reported unscheduled intravenous infusion
in the details of trial implementation. As this was
identified as our primary outcome, we sought out these
data and presented them as the primary analysis. We
believe that the analysis shows a clear effect. Our
approach highlights the value of paying careful
attention to the protocol for a systematic review before
examining the trials and illustrates how non-specialist
viewpoints can help obtain practical and useful
answers from a meta-analysis.

Cholera
We intended to examine treatment effects in patients
with and without cholera. A Cochrane review of rice
based rehydration compared with glucose oral
rehydration solution showed that rice water was
associated with lower stool volumes in cholera patients but
not in diarrhoea from other causes. The available data
were, however, insufficient. Three studies included
cholera patients, but separate data for cholera
patients were not available. We excluded two studies in
patients with cholera because they were in adults. Any
recommendation for rehydration treatment for
adults with cholera will need to take into account these
and any other trials found through careful systematic
searching.

Patients with cholera have severe loss of electrolytes. It is unclear, therefore, whether reduced osmolality
rehydration solution would be more effective than
standard WHO rehydration solution in these patients. The
reduced osmolality solution could increase the
risk of hyponatraemia and result in adverse clinical
events

Implications
Our study suggests that reduced osmolality rehydr-
ation solution should replace the WHO solution as the
standard treatment for dehydration caused by diarrhoea. Policymakers and clinicians may, however,
consider that the risk of hyponatraemia in patients with cholera outweighs the advantages of a reduced osmolality solution. One option would be to provide
standard WHO rehydration solution for people with
suspected cholera or in areas where cholera is prevalent. This is likely to be a logistical problem in
areas where diarrhoea is common and coexists with
cholera. The single formula sachet aids implementation
of this lifesaving intervention. Providing different
formulations complicates distribution and may impair
the effective delivery of any oral rehydration solution to
children. If policymakers decide not to use reduced osmolality solution in areas where cholera is common,
they must conduct a randomised controlled trial of the
two treatments in children with cholera to determine
whether the decision is correct.

This review will be maintained in the Cochrane Library.
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the process; and Dr Sheila Bird, Medical Research Council,
Cambridge, for her comments.

Contributors: SH and YK wrote the protocol, extracted, ana-
lysed and interpreted the data, and drafted the paper. PG
advised on inclusion criteria and outcomes for the protocol,
quality assessment, and analysis, and helped write the review. PG
is the guarantor.

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Competing interests: None declared.

What is already known on this topic
Oral rehydration solution prevents death from
diarrhoea in many developing countries

What this study adds
Children receiving a reduced osmolality
rehydration solution were less likely to need
intravenous infusion than those receiving WHO
rehydration solution

Reduced osmolality rehydration solution also
reduced stool output and vomiting

No difference was found in rates of hyponatraemia

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Neonatal convulsions after withdrawal of baclofen

B D M Ramayaka, H Dhaliwal, S Watkin, Department of Neonatal Medicine, City Hospital, Nottingham NG5 1PB

Baclofen is a skeletal muscle relaxant used for the relief of chronic severe spasticity resulting from disorders such as multiple sclerosis or traumatic injury to the spinal cord. It is used prophylactically to prevent convulsions in premature infants with a history of convulsions in the mother. We report convulsions in a 7 day old girl who had been exposed to baclofen during intrauterine life.

A paraplegic mother had been taking baclofen 20 mg four times daily (Lioresal, Novartis, Surrey), oxybutanin 3 mg three times daily, and trimethoprim 100 mg daily, which she continued throughout her pregnancy. The pregnancy was uneventful, but the baby was delivered by ventouse extraction owing to fetal tachycardia. The Apgar score was 10 at one and five minutes (cord pH: arterial 7.33, venous 7.3).

Seven days later the baby was admitted with generalised convulsions. In retrospect the mother had noticed abnormal movements from the second day after birth. Investigations included a full septic screen for bacteriology and virology; a full blood count; serum electrolytes; liver function tests; a metabolic screen of blood, urine, and cerebrospinal fluid; urine for toxicology; and cranial ultrasonography. All gave negative results. The convulsions did not respond to phenobarbitone, phenytoin, clonazepam, lignocaine, or pyridoxine, which were tried according to our hospital’s guidelines for the management of neonatal seizures. The baby received broad spectrum antibiotics until the cultures gave negative results. Electroencephalography on day 11 showed prolonged episodes of epileptic activity.

We thought that the convulsions could be due to withdrawal of baclofen. Baclofen, 1 mg/kg daily in four divided doses, was started. Thirty minutes after the first dose the convulsions stopped. Baclofen was withdrawn slowly over the next two weeks. Magnetic resonance imaging of the brain on day 17 suggested a short hypoxic ischaemic insult during the perinatal period.

Because the baby was in good condition at birth and because the convulsions were controlled within 30 minutes of starting baclofen, we concluded that the convulsions had been caused by its withdrawal. The change shown by the magnetic resonance image may have had secondary to the convulsions.

In adults the half life of baclofen is 2–6 hours (mean 3.5 hours). A previous report of baclofen overdose showed a secondary increase in baclofen concentrations into the therapeutic range after an initial decrease, probably due to its slow release from the central nervous system and lipid stores. This may explain the delay in presentation of our patient.

Convulsions after withdrawal of baclofen are well reported in adults. Convulsions after withdrawal of exposure to baclofen during intrauterine life have not been reported; this is the first such report to the Committee on Safety of Medicines.

Competing interests: None declared.


Drug points

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