ARTICLE

Enteral vs Intravenous Rehydration Therapy for Children With Gastroenteritis

A Meta-analysis of Randomized Controlled Trials

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Objective: To review the relative efficacy and safety of enteral vs intravenous (IV) rehydration therapy in treating childhood gastroenteritis.

Data Sources: MEDLINE, EMBASE, and the Cochrane Controlled Trials Register databases were searched. Known investigators and expert bodies were contacted to locate unpublished and ongoing studies.

Study Selection: Studies were selected based on the following criteria: randomized or quasi-randomized trials; children younger than 15 years with a clinical diagnosis of gastroenteritis of less than 1-week duration; interventions comprising enteral and IV treatment arms; and at least 1 of the following: major adverse event rates, treatment failure rates, weight gain with treatment, measurement of ongoing losses, length of hospital stay, costs of treatment, and satisfaction with treatment.

Data Extraction: Data were extracted from eligible studies, which were then combined using a random-effects model.

Data Synthesis: Sixteen trials involving 1545 children and conducted in 11 countries were identified. Compared with children treated with IV rehydration, children treated with oral rehydration had significantly fewer major adverse events, including death or seizures (relative risk, 0.36; 95% confidence interval [CI], 0.14-0.89), and a significant reduction in length of hospital stay (mean, 21 hours; 95% CI, 8-35 hours). There was no difference in weight gain between the 2 groups (mean, −26 g; 95% CI, −61 to 10 g). The overall failure rate of enteral therapy was 4.0% (95% CI, 3.0%-5.0%).

Conclusions: For childhood gastroenteritis, enteral rehydration is as effective if not better than IV rehydration. Enteral rehydration by the oral or nasogastric route is associated with significantly fewer major adverse events and a shorter hospital stay compared with IV therapy and is successful in most children.

Arch Pediatr Adolesc Med. 2004;158:483-490

ACUTE GASTROENTERITIS IS one of the most common illnesses affecting infants and young children. Rates of hospitalization with gastroenteritis for children younger than 5 years have been reported to be 9 per 1000 per year in the United States[1] and 12 to 15 per 1000 in England[2] and Australia.[3] In developing countries, the rates of hospitalization with gastroenteritis are known to be higher (for example, 26 per 1000 per year in China[4]).

Since the 1970s, pediatric authorities have recommended enteral rehydration as the preferred treatment for fluid and electrolyte losses in gastroenteritis.[5-7] Case-control studies from this period have demonstrated that oral rehydration was equally effective when compared with intravenous (IV) therapy.[8,9] However, despite these recommendations, oral rehydration has repeatedly been described as "the underused simple solution,"[10] because IV rehydration and hospitalization are still often chosen over oral rehydration, particularly in the developed world.[11] A large, multicenter, European study[12] found that 80% of children hospitalized with gastroenteritis had less than 5% dehydration, and this has also been observed among hospitalized children in Australia.[13] Yet 82% of the

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Australian children[13] and 94% of children in a recent 18-hospital, Canadian study[14] received treatment with IV rehydration.

There has been 1 previous systematic review on this topic. In 1996, Gavin et al[15] published a systematic review of trials comparing oral rehydration therapy with IV rehydration in well-nourished children with

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childhood gastroenteritis. They reviewed 6 randomized controlled trials and found a combined oral rehydration therapy failure rate of 3.6% but did not combine data for other outcome measures. Our aim for this study was to compare the relative benefits and harms of enteral vs IV rehydration when treating childhood gastroenteritis.

METHODS

DATA SOURCES

We searched MEDLINE (from 1966 to June 2003), EMBASE (1988 to June 2003), and the Cochrane Controlled Trials Register (Issue 2, 2003) databases. We used a combination of medical subject headings (*gastroenteritis, vomiting, cholera, fluid therapy, oral rehydration, intravenous therapy, IV therapy, intravenous, infusions, enteral nutrition*) and text words (*diarrh?ea, nasogastric feed$, rehydration solution$*). This search was then restricted using the methods developed by the Cochrane Collaboration to select only randomized controlled trials.[16] We hand-searched citation lists of all trials identified by these methods. Two reviewers (B.K.F. and A.H.) independently assessed all identified trials. Where the reviewers did not agree, differences were resolved by discussion.

For information on unpublished data and ongoing trials, we contacted known investigators within the field. We also contacted the following international expert bodies: American Academy of Pediatrics Subcommittee on Acute Gastroenteritis, European Society of Paediatric Gastroenterology and Nutrition Working Group on Acute Diarrhoea, World Health Organisation Programme for Control of Diarrhoeal Disease, and International Centre for Diarrhoeal Diseases Research.

STUDY SELECTION

Trials were included for analysis if they met the following predetermined criteria: (1) randomized or quasi-randomized trials; (2) children younger than 15 years with a clinical diagnosis of gastroenteritis of less than 1-week duration; (3) interventions comprising both enteral and IV treatment arms; and (4) at least 1 of the study outcomes of interest. Study outcomes of interest were major adverse event rates (seizure or death), treatment failure rates, weight gain with treatment, measurement of ongoing losses, length of hospital stay, costs of treatment, and satisfaction with treatment. Failure of enteral therapy was defined as subsequent rehydration with IV fluid therapy. We included studies without language restriction.

VALIDITY ASSESSMENT

Journal and author identities were not concealed from the reviewers. The quality of each included trial was assessed using the following criteria: methods of allocation concealment, blinding of outcome assessment, postrandomization exclusions, completeness of follow-up, blinding of data analysis, and intention-to-treat analysis.

DATA ABSTRACTION

Two reviewers (B.K.F. and A.H.) independently extracted data for each outcome from the included trials. The data were then compared, and any differences between reviewers were resolved by discussion.

STUDY CHARACTERISTICS

The characteristics of the participants were classified by age, nutritional status, degree of dehydration, and geographic location. The type, route, and rate of enteral and parenteral therapy were recorded (**Table**).

QUANTITATIVE DATA SYNTHESIS

For individual trials, the relative risk (RR) was calculated for binary outcomes and the mean difference for continuous outcomes. The 95% confidence intervals (CIs) were calculated for all outcomes. We assessed homogeneity between trials using the Cochran Q statistic, with $P<.10$ indicating significant heterogeneity. Summary estimates of effect were estimated using the random-effects model. Funnel plots were constructed to check for possible publication bias. Statistical analysis was conducted using Revman 4.1 statistical software.[16] We tested for possible sources of heterogeneity (type, rate, and route of rehydration treatment; nutritional and dehydration status of patients; and age) by subgroup analysis.

RESULTS

TRIAL FLOW

From 841 abstracts identified as potentially suitable for consideration, 21 full-text publications were reviewed.[17-37] Six studies[32-37] were excluded, because they did not meet the described inclusion criteria, leaving 15 included studies[17-31] (**Figure 1**). One[27] of the 15 published studies comprised trials in 2 separate countries, which we considered separately, leaving a final count of 16 trials, including data from 1545 children from 11 countries for analysis.

STUDY CHARACTERISTICS

Half of the trials were conducted in developing countries, and half had 90 or more participants (Table). Five trials[18,21,23,28,29] included children with severe dehydration, and 2 included children who were malnourished.[21,28] Three studies[17,25,31] included children older than 3 years. Regarding type of enteral therapy, 10 trials[17-19,22,23,25,27,29,30] compared oral with IV and 3 trials[20,26,28] compared nasogastric with IV rehydration. The remaining 3 trials[21,24,31] used a combination of enteral routes.

Trials generally compared variable osmolality enteral rehydration solution with an isotonic parenteral solution. Two trials[24,28] used low osmolality enteral solutions (≤270 mOsm/L), 10 trials[18,20,22,23,25,26,29-31] used World Health Organization–recommended enteral solutions (≥300 mOsm/L), and the remainder used both strengths and compared them with IV rehydration. No trial used food-based rehydration as initial enteral therapy. The rates of fluid administration between treatment arms were equivalent for 11 of the 16 trials.

In 5 trials,[18,19,21,27] IV rehydration was compared with several enteral rehydration groups, each using fluid of variable sodium concentration, between 20 and 90 mM. Where this occurred, there were no significant differences in outcomes between multiple enteral rehydration groups. For these trials, therefore, we calculated a combined standard deviation for all enteral rehydration groups (derived from the individual group standard deviations), after computing the new mean, total sample size, and the sum of the squared observations.[38]

Characteristics of Included Studies

Source, y	Setting/Age, y	Initial Enteral Fluid Therapy: Enteral Group, No.	Sodium Concentration, mM: 20-40	45-60	75-90	Fluid Rate, mL/kg/h	Nasogastric Rehydration	Initial IV Fluid Therapy: IV Group, No.	Sodium Concentration, mM: 100-150	75	30	Fluid Rate, mL/kg/h	Fasting Period, h
Singh et al,[29] 1982	Afghanistan/≤2	50		✓		8	No	50		✓		8	
Santosham et al,[27] 1982	United States/≤2	15		✓		11	No	17		✓		7	12-24
		20			✓								
Santosham et al,[27] 1982	Panama/≤2	33		✓		7	No	31		✓		11	8
		30			✓								
Tamer et al,[30] 1985	United States/≤3	50			✓	22	No	50	✓			11	18-24
Sharifi et al,[28] 1985	Iran/≤2	236			✓	40	All	234	✓			20-30	
Listernick et al,[23] 1986	United States/≤2	15		✓		20	No	14	✓			20	
Hernandez et al,[21] 1987	Colombia/≤2	36	✓			20-30	Some	36	✓			20-30	
		36		✓									
		36			✓								
Vesikari et al,[31] 1987	Finland/≤5	22		✓		9	Some	15	✓			20-30	12
Brown et al,[18] 1988	Peru/≤3	31	✓			6	No	34	✓			9	48
		29	✓										
		34	✓										
Martin de Pumarejo et al,[25] 1990	Puerto Rico/≤4	17			✓	10-20	No	14	✓			5	12-24
Mackenzie and Barnes,[24] 1991	Australia/≤3	57		✓		10	Some	54			✓	8	
Issenman and Leung,[22] 1993	Canada/≤3	22		✓		20	No	18	✓			20	12
el-Mougi et al,[19] 1994	Egypt/≤2	20		✓		10	No	20		✓		8	4-6
		21			✓								
Gremse,[20] 1995	United States/≤2	12			✓	8	All	12		✓		8	
Nager and Wang,[26] 2002	United States/≤3	46		✓		17	All	44	✓			17	3
Atherly-John et al,[17] 2002	United States/≤17	18		?		4-6	No	16	✓			20	

Abbreviation: IV, intravenous.

STUDY QUALITY

Overall, trial quality was variable, with incomplete reporting of trial methods common. In particular, no study reported blinding of data analysis, and only 3 studies[17,18,24] described adequate randomization and allocation concealment. Although several studies implied that analysis of results was on an intention-to-treat basis and follow-up of subjects may have been complete, this was not explicitly stated for any study.

OUTCOMES

For several trials, data were not able to be combined for analysis, because no variance was given for outcomes[23,24,26] or some outcomes (eg, weight gain measurements[30,31]) had skewed results. Funnel plot symmetry was examined for all outcome measures, but no meaningful analysis was possible due to the small number of studies. There were inadequate data for subgroup analysis by age, nutritional status, or degree of dehydration.

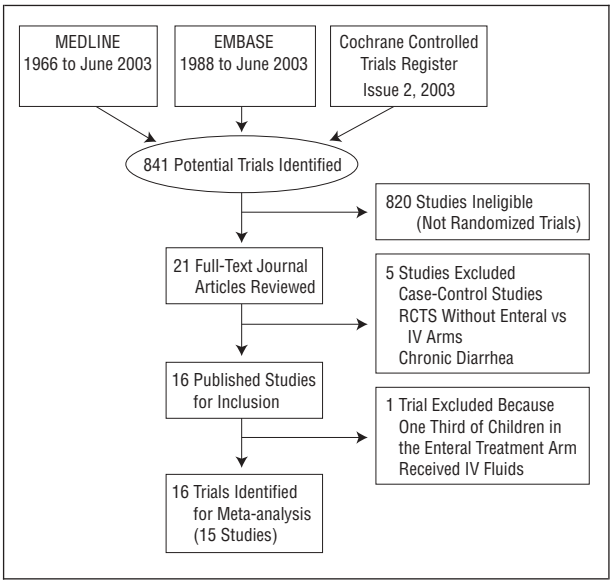

Figure 1. Selection of randomized controlled trials (RCTs) in childhood gastroenteritis. IV indicates intravenous.

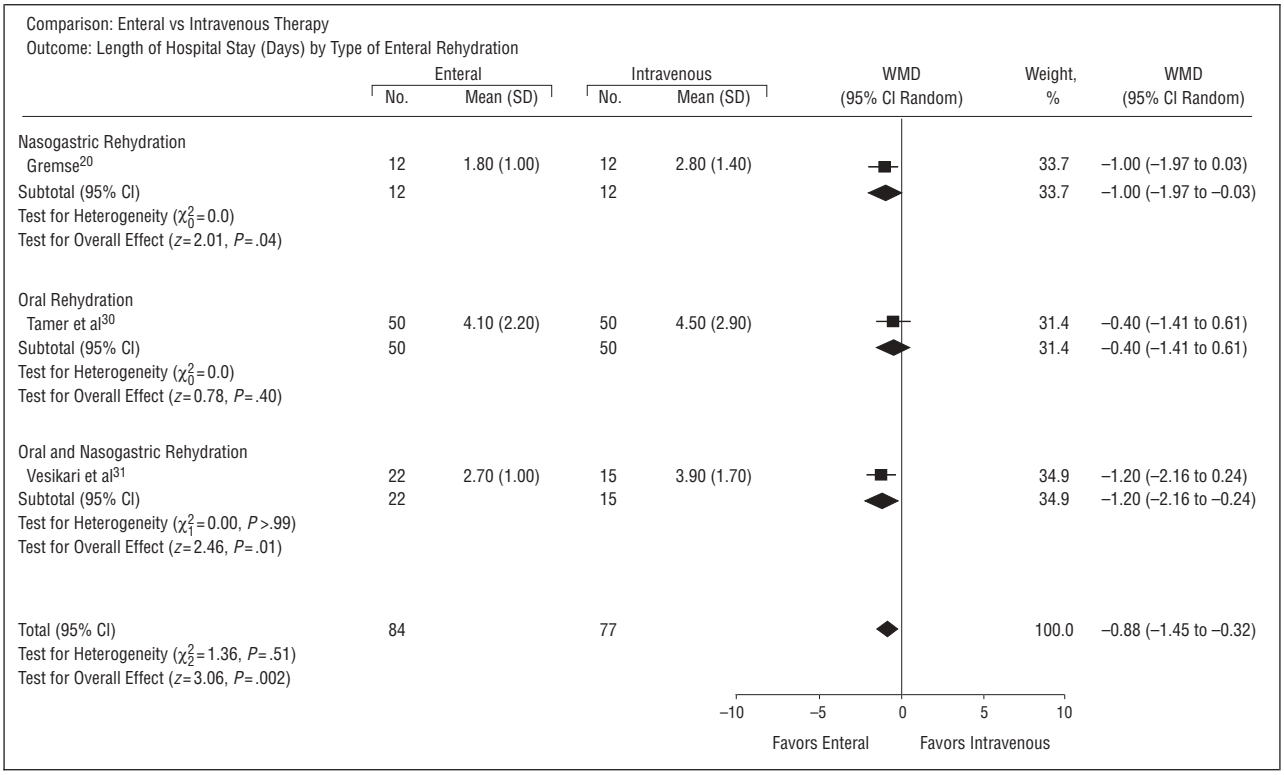

Figure 2. Length of hospital stay by type of enteral rehydration. CI indicates confidence interval; WMD, weighted mean difference.

LENGTH OF HOSPITAL STAY

All 5 studies reporting data were in developed countries. In 3 trials[20,30,31] with 161 participants, patients receiving enteral rehydration had a significantly reduced hospital stay by 21 hours (95% CI, 8-35 hours). There was no significant heterogeneity (P=.51) (**Figure 2**). Two studies were not included in the pooled analysis due to lack of variance data. Listernick et al[23] found enterally rehydrated children had a reduced mean hospital stay of 29 hours compared with the IV group. Mackenzie and Barnes[24] found no statistically significant difference in median length of hospital stay between the 2 treatment groups. For the study by Mackenzie and Barnes,[24] the oral rehydration group had greater intestinal losses and higher rates of antibiotic treatment at trial commencement.

WEIGHT GAIN

Nine trials[19,22-24,27,28,30,31] gave information on weight gain at discharge from hospital. Three trials did not contribute to the summary estimate, because they either had skewed data[30,31] or reported only median values,[24] but these 3 studies showed no significant difference in weight gain between children rehydrated by IV or enteral methods.

Six trials could be considered for a summary estimate, but there was significant heterogeneity between studies (P=.001) (**Figure 3**). Considering the 1 trial in undernourished children as a separate population type, there was no heterogeneity between the remaining 5 trials[19,22,23,27] in well-nourished children (276 participants). These 5 trials showed no significant difference in weight gain when comparing those rehydrated enterally with those rehydrated intravenously (mean, −26 g; 95% CI, −61 to 10 g). The 1 trial in undernourished children[27] used obligate nasogastric rehydration at an accelerated rate of 40 mL/kg per hour, and this showed a modest weight gain in those receiving enteral rehydration (mean, 80 g; 95% CI, 45-115 g).

DURATION OF INTESTINAL LOSSES

Eight trials[18-20,27-29,31] (946 patients) provided information on duration of diarrhea. There was heterogeneity among all studies, but this was explainable by separating studies comparing IV with oral rehydration and those comparing IV with nasogastric rehydration (**Figure 4**). For the 5 trials[18,19,27,29] comparing IV with oral rehydration, there was no significant difference in duration of diarrhea, and there was no heterogeneity between the studies (P=.95). Combining the 3 trials using nasogastric[20,28] or oral and nasogastric rehydration,[31] there was a significant reduction in duration of diarrhea (mean, 23 hours; 95% CI, 11-36 hours), with no evidence of heterogeneity between the studies (P=.20). One study[20] measured duration of vomiting and found no significant difference between treatment groups.

QUANTITY OF INTESTINAL LOSSES

Six trials provided information on volume[18,19,27,31] or frequency[30] of stool output. These studies showed significant heterogeneity (P<.001), which was not explainable. Four[18,19,27,30] of the 6 studies (United States arm[27]) found significantly reduced stool output in children receiving IV therapy compared with those enterally rehy-

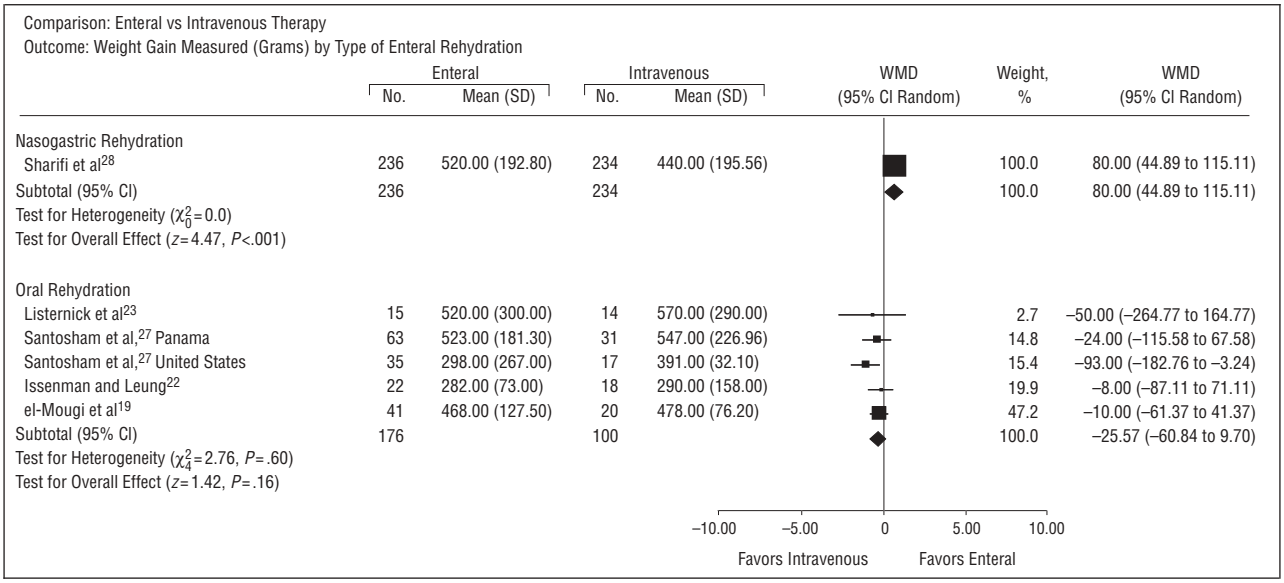

Figure 3. Weight gain at discharge by type of enteral rehydration. CI indicates confidence interval; WMD, weighted mean difference.

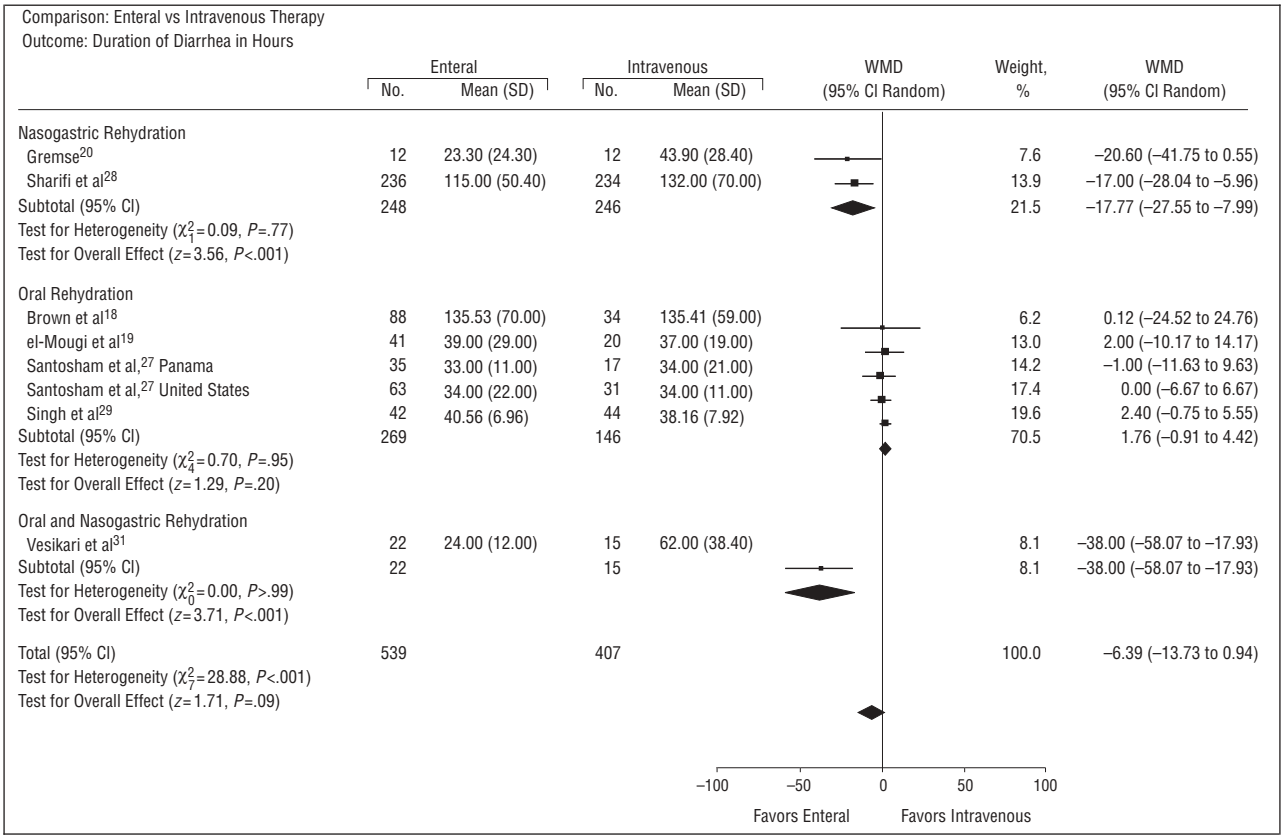

Figure 4. Duration of diarrhea by type of enteral rehydration. CI indicates confidence interval; WMD, weighted mean difference.

drated, even though 3 of these studies[18,19,27] (Panama arm[27]) had found no associated reduction in the duration of diarrhea. The other 2 studies[27,31] (Panama arm[27]) reporting stool output showed no difference between treatments. In all 6 studies, children in the IV rehydration group fasted for 6 to 48 hours.

FAILURE RATES

The combined failure rate of enteral rehydration therapy across the 16 trials (1545 participants) was 4.0% (95% CI, 3.0%-5.0%). The failure rate was 3.3% (6 trials) in children treated with nasogastric rehydra-

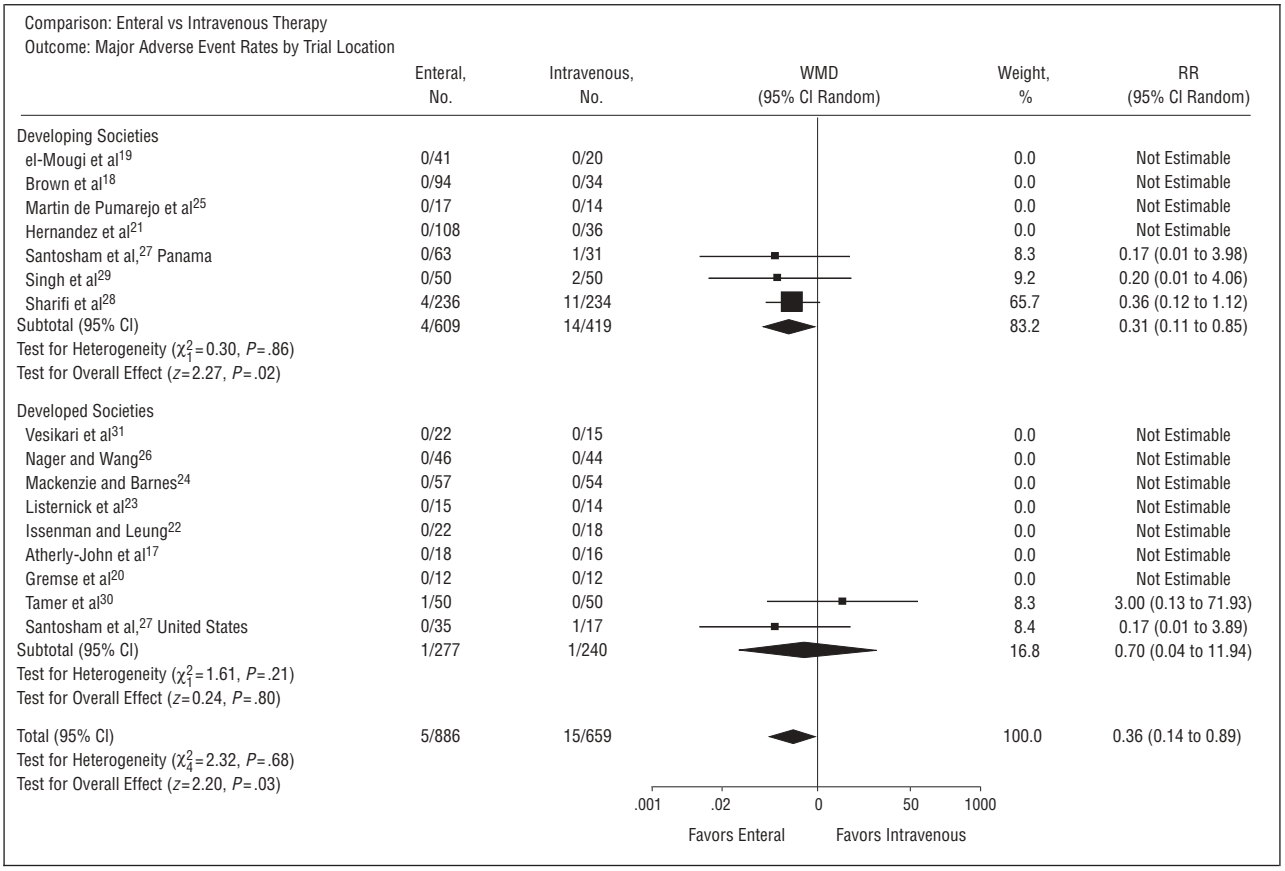

Figure 5. Major adverse event rates by trial location. CI indicates confidence interval; RR, relative risk and WMD, weighted mean difference.

tion compared with 4.7% (10 trials) in children rehydrated orally. By definition, there was no failure rate for IV therapy.

MAJOR ADVERSE EVENTS

Major adverse events (death or seizure) occurred in 5 of the 16 trials providing data for this outcome[27-30] (**Figure 5**). The studies considered showed no evidence of heterogeneity (*P*=.68). There were significantly fewer major adverse events for enterally rehydrated children (RR, 0.36; 95% CI, 0.14-0.89). The study by Sharifi et al[28] largely influenced this result, with 7 deaths and 8 seizures (and 66% of the overall weighting). This trial enrolled a severely affected population, in which one third of the children were below the third centile for weight and more than 20% had evidence of shock at admission. Reanalysis without the study by Sharifi et al[28] showed a similar risk, but this was no longer statistically significant (RR, 0.35; 95% CI, 0.07-1.68).

There were no deaths among patients treated in developed countries. There was an equal chance of seizure of 0.4%, with treatment by either enteral or IV rehydration. For the 2 patients who experienced this complication, this was not due to an identifiable abnormality.[26,29] Minor adverse events (phlebitis, electrolyte abnormality, facial edema) were incompletely reported across studies and could not be reliably compared between groups.

OTHER OUTCOME MEASURES

Only 3 US studies reported costs but with inadequate detail to combine results. Hospital-based treatment with IV therapy was twice as costly in 2 studies[20,23] and incurred 18% more cost in 1 other study.[26] One trial reported rates of "high satisfaction with treatment"[17] and found that two thirds of those orally rehydrated and one third of those intravenously rehydrated were highly satisfied with all aspects of the hospital visit, and this was a significant difference.

COMMENT

In children with acute gastroenteritis, available evidence shows that enteral rehydration is associated with reduced length of hospital stay and fewer major adverse events compared with treatment with IV rehydration. Failure of enteral rehydration is generally low. When comparing the 2 routes of treatment, there was no significant clinical difference in measured intestinal losses or weight gain across trials.

Hospital stay was significantly reduced in children treated with enteral rehydration. This may have been due to an early reintroduction of diet for children treated enterally, whereas those receiving IV fluids often fasted for a longer period. A previous European, multicenter study[12] found that early refeeding was associated with increased weight gain but not with reduced length of hos-

pital stay. Compared with the only previously published systematic review by Gavin et al,[15] we included an additional 10 trials. Gavin et al[15] have described a reduced length of hospital stay for only 1 of 4 studies they had reviewed. Nine studies[17,21-23,25,26,28,30,31] used rates of IV fluid therapy considered to be rapid rehydration (>10 mL/kg hourly), which from small uncontrolled trials seemed to be well tolerated and associated with early discharge from the hospital.[39-41]

There was no consistent association between recovery from diarrhea (as measured by duration of diarrhea and volume of stool output) and type of rehydration therapy across studies. Duration of diarrhea was significantly shorter in children treated with nasogastric but not oral rehydration when each was compared with IV therapy. Volume of stool output, however, was generally reduced in children rehydrated intravenously, and this treatment group fasted for a variable period across all studies. These differences could not be explained on the basis of patient characteristics or disease severity but may have been due to the varying regimens of dietary reintroduction or trial conduct between treatment arms. A previous systematic review by Hahn et al[42] found reduced osmolality enteral therapy was associated with reduced diarrhea and vomiting, but this was not seen among the studies we included.

Children receiving nasogastric fluids had significant weight gain compared with IV treatment groups, but there was no difference for children treated with oral fluids. These findings of shorter duration of diarrhea and greater weight gain in nasogastrically fed children were dominated by the study by Sharifi et al[28] in which this effect may have been due to the accelerated nasogastric rehydration and earlier refeeding for their enteral treatment group. Apart from this trial, the overall conclusion when considering recovery from diarrhea and weight loss is that enteral and IV rehydration produce benefits that are not different.

Across the 16 trials, there was a significant reduction in major adverse events for enterally rehydrated children. For developing countries, we calculated that for every 37 children treated with enteral rather than IV rehydration, there was 1 fewer seizure or death complicating treatment. This finding was most pronounced in the study by Sharifi et al[28] among high-risk children with significant comorbidity, where the deaths occurred 3 to 8 days after hospitalization and were reported to be unrelated to biochemical abnormalities. For developed countries, the risk of seizures from rehydration treatment was approximately 1 in 250, irrespective of the treatment method used.

Combining data from all studies in this review, enteral therapy failed in 4.0% of children who were dehydrated with gastroenteritis. This is similar to data from the study by Gavin et al[15] and from other multicenter trials[12] and supports the recommendation from the American Academy of Pediatrics that "almost all children who have vomiting and dehydration can be treated with oral rehydration therapy."[5]

Pediatric authorities from Europe and Canada[6,7] have promoted the same recommendations, because IV therapy remains the preferred treatment for mild and moderately dehydrated children.[13,14] A major barrier to acceptance of enteral therapy may be related to the patient, parent, or staff reluctance to accept these recommendations. Several researchers observed that reluctance from parents and children toward enteral rehydration was easily overcome[23,25,29]; however, 2 studies[22,24] identified considerable resistance from nursing and medical staff. One study[17] surveyed satisfaction with type of rehydration therapy, and their results showed a marked parental preference for oral rehydration.

The strength of the conclusions for this review is limited by several factors. We were unable to perform subgroup analysis by study quality, because details of trial methods were not provided by any study. Heterogeneity in results across the studies was explainable by variations in treatment or patient populations, suggesting that quality was an unlikely cause of variability in trial results. In addition, due to skewed results or no data on variance being provided, not all trials contributed to all outcomes. However, the direction of these individual results and the summary effect measure were generally concordant. Although all studies provided general participant characteristics, without individual data it was difficult to make meaningful subgroup comparisons (by age, nutritional status, severity of dehydration, and presence of electrolyte abnormalities). Finally, we were unable to test for publication bias due to the relatively small number of trials.

IMPLICATIONS FOR FURTHER RESEARCH

When treating dehydration in children with gastroenteritis, IV therapy provides little benefit over oral or nasogastric rehydration. There seemed to be no difference in treatment effect when comparing oral with IV over oral with nasogastric rehydration, although nasogastric rehydration would be regarded as more invasive and unpleasant than IV therapy by many practitioners. The continuing preference for IV rehydration in many developed countries may be due to factors not yet identified, and the threshold for rejection of oral therapy by medical and nursing staff is an important issue that remains unexplored. Intravenous therapy may be regarded as "better" simply because it cannot be performed at home, and health care practitioners wish to provide something extra after oral rehydration has been attempted by parents.

With the limited evidence available, we found a reduced length of hospital stay when children received enteral rehydration. With gastroenteritis being one of the most common reasons for hospitalization of children, there are major implications for resource utilization, but we were unable to do a formal trials-based economic evaluation to quantify the savings provided by enteral rather than IV therapy.

CONCLUSIONS

There is no evidence to support the ongoing use of IV therapy for the first-line management of most cases of childhood gastroenteritis. Practitioners who treat this condition need to address the obstacles, which currently prevent a wider acceptance and use of enteral rehydration.

What This Study Adds

Since the 1970s, professional bodies have promoted enteral rehydration treatment for childhood gastroenteritis. A limited systematic review in 1996 confirmed the low failure rate of enteral rehydration, yet intravenous rehydration remains the preferred treatment in many countries. We sought to comprehensively update the relative benefits and harms of rehydration therapy for gastroenteritis in all communities.

We identified 16 trials in developing and developed countries. Enteral rehydration by oral or nasogastric routes is associated with fewer major adverse events and a shorter hospital stay. The low rate of failure with enteral therapy (4.0%) suggests that we need to address other cultural obstacles that prevent a wider acceptance of enteral rehydration.

Accepted for publication December 29, 2003.

Each author made a substantial contribution to the design of the study, the analysis and interpretation of the data, and comments on the style and content of the final manuscript.

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