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Risk factors for fatal diarrhoea among dehydrated malnourished children in a Madagascar hospital

N. Ravelomanana[1], O. Razafindrakoto[1], D. R. Rakotoarimanana[1], A. Briend[2,3], J. F. Desjeux[2] and J. Y. Mary[4]

/Briend, A. André

[1]*Service de Pédiatrie B, Hôpital de Befelatanana, Antananarivo, Madagascar;* [2]*INSERM U290, Paris;* [3]*seconded by ORSTOM, Paris;* [4]*INSERM U263, Paris*

Objective: To examine mortality risk factors during rehydration among 6–35 month malnourished children with diarrhoea.
Design: Data collected prospectively during a clinical trial comparing two oral rehydration solutions (ORS).
Setting: Paediatric ward.
Subjects: Study children had either a weight-for-age Z-score below –2 or a weight-for-height below 70% of NCHS median. All had diarrhoea for <5 days. 150 were enrolled and two were excluded for intercurrent infection.
Intervention: Children were randomly allocated to receiving 100 ml/kg of standard or rice-based ORS during the 6 h following admission. Then they received 420 kJ/kg/day of high energy milk, progressively increased to 840 kJ/kg/day.
Results: Mortality rate was 16% and with no difference by ORS group. In univariate analysis, the risk of dying (mean odds ratio; 95% confidence interval) was significantly higher among girls (3.5; 1.4–8.9), in non-breast-fed children (3.7; 1.4–9.6) and in children with a low weight-for-height (5.1; 1.9–14.1). Low weight, moderate or severe dehydration, low plasma specific gravity or total plasma protein and longer duration of diarrhoea before inclusion also were significant risk factors. In multivariate logistic analysis, only absence of breast-feeding was associated with a higher risk of dying among girls with a low weight-for-height. Among them, eight out of nine died, compared to 15 out of 139 for other children.
Conclusion: Breast-feedings protected severely malnourished girls against death from diarrhoea even when dehydration was corrected. Mechanisms underlying this selective effect are poorly understood.
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Descriptors: breast-feeding, diarrhoea, malnutrition, mortality

Introduction

Recommendations regarding rehydration of severely malnourished children are conflicting. For instance, sodium concentration of currently recommended oral rehydration solutions for malnourished children varies from 30–35 to 90 mEq/l (WHO CDD Programme, 1990; Viteri, 1991; Waterlow, 1992; Briend & Golden, 1993). It has been argued that standard WHO

Correspondence to: Dr Jean Yves Mary, INSERM U 263, Centre de Bioinformatique, Université Paris 7, T53, 2 place Jussieu, 75251 place Jussieu, 75251 Paris Cedex 05, France.

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oral rehydration solutions (ORS) are not adapted to treatment of dehydration in severely malnourished children (Waterlow, 1992; Briend & Golden, 1993) because malnutrition influences hydroelectrolytic changes occurring in cases of diarrhoea. Compared to well-nourished children, potassium depletion is more pronounced, hyponatraemia is more frequent but sodium retention is more important during rehydration (Hirschhorn, 1980; Marin *et al.*, 1986; Waterlow, 1992) and a low sodium-high potassium oral rehydration solution might be more appropriate.

The high risk of dying associated with different degrees of malnutrition in cases of diarrhoea is well documented (Briend *et al.*, 1986; Beau *et al.*, 1987). Few studies, however, examined individual risk factors associated with the risk of dying among dehydrated malnourished children receiving a standard rehydration therapy. Recently, we carried out a prospective controlled randomized trial comparing the efficacy of rice-based ORS with that of the standard WHO solution in malnourished children (Razafindrakoto *et al.*, 1991; Razafindrakoto *et al.*, 1993). Both solutions had the WHO-recommended electrolyte concentrations, namely 90 mEq/l for sodium and 20 mEq/l for potassium. Mortality during this trial was higher than expected in well-nourished children treated for dehydration. Data collected during this study were used to examine factors associated with the risk of dying during a well-defined hospital treatment for dehydrated malnourished children and especially factors related to water and electrolyte status.

Patients and methods

Inclusion criteria

Children included in this study were 6–35 months old. Their weight-for-age *Z*-score on admission was below –2 and/or their weight-for-height was below 70% of the median of the National Center for Health Statistics (NCHS) (WHO working group, 1986). They had a non-bloody diarrhoea lasting for <5 days. Children with major illness, such as meningitis, malaria, severe pneumopathy or tuberculosis were excluded from the study. Children with oedema were also excluded. Every study day, only the first two malnourished patients fulfilling selection criteria were included in the study.

Clinical management

Dehydration was treated according to WHO guidelines (World Health Organization, CDD programme, 1990) by giving 100 ml/kg body weight of ORS during the first 6 h until rehydration was completed. Dehydration status was determined hourly. After the first 6 h, the same therapeutic scheme was continued if the child was still dehydrated. After rehydration was completed, children were given 1 volume of plain water for 2 volumes of ORS. There was no significant difference in ORS intake between children receiving either rice-based or WHO ORS (Razafindrakoto *et al.*, 1993).

Children received either WHO ORS or rice-based ORS through random allocation. These two groups, however, were pooled for this analysis since no significant difference was found between them regarding baseline data, mortality rate (15% and 16% respectively) and follow-up duration.

Starting 4 h after admission, children were given high energy milk (4,2 kJ/ml) made of dried skimmed milk, oil and sugar up to a total of 420 kJ/kg body weight. This quantity was increased to 840 kJ/kg body weight during the first week, with local diet being introduced progressively from the 3rd day.

Antimalarial tablets and antibiotic treatment were prescribed to children with any sign of intercurrent infections. Altogether, 125 children (85%) received antibiotics. Patient follow-up was achieved up to diarrhoea cessation and discharge. The only exceptions were patient withdrawal or patient death.

All children were attended by their mothers at hospital up to discharge.

Data collection

On admission, data regarding history of illness and breast-feeding status were collected from the mother. Dehydration status was assessed and the weight and height of nude children were recorded. Blood electrolytes, total plasma proteins, haematocrit and plasma specific gravity were also measured. For children who died during the study, the likely cause of death was determined from clinical records.

Statistical analysis

First, the distribution of criteria measured at inclusion into the trial were compared between the group of children who died and the group of

Table 1. Characteristics of the studied sample at hospital admission

	Mean ± *SD*	*Median*	*n*
Age (months)	15 ± 14	14	147
Weight on admission (g)	6000 ± 1250	5915	148
Weight 6 h after admission (g)	6150 ± 1280	6120	148
Weight gain (%)	2.61 ± 2.28	2.22	148
Height (cm)	69 ± 6	68	148
Weight-for-age (% NCHS)	58 ± 9	57	147
Weight-for-height (% NCHS)	75 ± 8	76	148
Duration of diarrhoea before admission (days)	2.8 ± 1.2	3.0	148
Number of stools/24 h before admission	8 ± 4	7	148
Number of vomits/24 h before admission	3.5 ± 2.5	3.0	82
Haematocrit (%)	36 ± 7	36	148
Plasma Na (mEq/l)	122 ± 13	124	132
Plasma K (mEq/l)	3 ± 1	3	131
Total plasma proteins (g/l)	51 ± 11	51	144
Plasma specific gravity	1.064 ± 0.011	1.064	134
Reducing sugars in stools (g/24 h)	8.7 ± 13.4	2.9	124
	%	*n*	
Female	40	148	
Breast-feeding			
Before diarrhoea	62	148	
24 h before admission	57	148	
Moderate or severe dehydration	74	148	
Fever before admission	57	148	
Vomiting before admission	55	148	

those who survived up to diarrhoea cessation. This comparison was performed through χ^2-test for qualitative criteria and Mann–Whitney *U*-test for quantitative criteria (Siegel, 1956). Furthermore, if a significant difference was observed between these two groups, continuous variables were converted to dichotomous variables using either the median or the 16th centile as cut-off points (the 16th centile corresponding to the proportion of children who died during the study). Odds ratios [mean and 95% confidence interval (CI)] were calculated for all risk factors using the univariate logistic regression model (Cox, 1970).

In a second step, all variables which were possibly associated with the risk of dying ($P <$ 0.20 in the univariate analysis) were examined by using the multivariate logistic regression method and tested through the maximum likelihood ratio test between different logistic regression models (Kleinbaum, Kupper & Morgenstern, 1982).

In a third step, all these analyses were repeated when the data of five children who died before discharge, but after diarrhoea cessation, were included in the group of children who died.

Results

Among the 150 children included in the trial, two were withdrawn: one had urinary infection and the other pulmonary tuberculosis. The characteristics of the studied sample are shown in Table 1.

Twenty-three children died before diarrhoea cessation (Table 2). There was no clearly predominant cause of death. None of the death was associated with presence of oedema.

For surviving children, duration of diarrhoea varied between 9 and 249 h (mean ± SD = 78 ± 42 h). Discharge of patients from hospital occurred at least 24 h after the end of the diarrhoeal episode with a median delay of 114 h, except for the five children who died before discharge within the 2 days following diarrhoea cessation.

Comparisons of the distribution of variables measured at admission between children who survived and those who died before diarrhoea

Table 2. Cause of death among study patients

Randomization number	*Time between admission and death (hours)*	*Treatment*	*Cause of death*
(a) Before diarrhoea cessation			
132	9	WHO-ORS	Pneumonia
25	21	WHO-ORS	Aspiration pneumonia
138	21	Rice-ORS	Unexplained sudden death
150	27	WHO-ORS	Renal failure
103	29	Rice-ORS	Dehydration
92	31	WHO-ORS	Respiratory distress and dehydration
127	31	WHO-ORS	Respiratory distress and abdominal distension
33	34	Rice-ORS	Convulsions and dehydration
131	47	Rice-ORS	Respiratory distress
79	52	Rice-ORS	Unexplained sudden death
54	79	WHO-ORS	Vomito negro and bronchiolitis
110	79	Rice-ORS	Vomito negro and laryngitis
19	84	Rice-ORS	Respiratory distress
101	86	Rice-ORS	Respiratory distress
64	89	WHO-ORS	Suspected whooping cough
109	91	Rice-ORS	Unexplained sudden death
102	103	WHO-ORS	Bronchiolitis and abdominal distension
135	116	WHO-ORS	Candidal infection
108	119	Rice-ORS	Candidal infection
134	171	WHO-ORS	Respiratory distress and convulsions
123	197	Rice-ORS	Respiratory distress and intoxication by herbal medicine
78	240	WHO-ORS	Candidal infection
10	249	Rice-ORS	Candidal infection
(b) After diarrhoea cessation before discharge			
57	116	Rice-ORS	Unexplained sudden death
35	153	Rice-ORS	Bronchiolitis and convulsions
116	172	WHO-ORS	Anaemia and malaria
95	194	Rice-ORS	Bronchiolitis and oral thrush
29	212	Rice-ORS	Unexplained sudden death

cessation are shown in Table 3. Children who died were lighter and more frequently malnourished (lower weight and weight-for-height) than those who survived. They had on average a lower total plasma protein and plasma specific gravity. Absence of breast-feeding before the onset of diarrhoea or during the episode before admission, moderate or severe dehydration and longer duration of diarrhoea before admission were significantly associated with the risk of dying. Odds ratios of risk factors significantly associated with the risk of dying are reported in Table 4.

Multivariate analysis showed that among all these factors, only the absence of breast-feeding, low weight-for-height and being a female were significantly associated with a high risk of dying. All biological factors which appeared to be significantly related to mortality in the univariate analysis were rejected from the multivariate analysis as soon as weight-for-height was introduced in the model. The final model, however, showed that breast-feeding, sex and malnutrition were significant only as interaction terms ($P < 0.001$), which means that absence of breast-feeding was significantly associated with a higher risk of dying only among girls with a low weight-for-height. In the category of non-breast-fed malnourished girls, eight deaths were observed in a total of nine children, whereas 15 deaths were observed among the 139 other children. In contrast, among non-breast-fed malnourished boys, one death was observed in a total of seven children. A borderline non-significant term ($P < 0.06$) suggested a group with a favourable outcome, namely breast-fed boys, with only three deaths among 54 children.

Table 3. Comparison of children who died and of those who survived during hospital treatment

	Survived *Mean ± SD (n)*	*Died* *Mean ± SD (n)*	*P*
Age (months)	15.5 ± 7.2 (124)	14.7 ± 8.0 (23)	0.479
Weight on admission (g)	6070 ± 1240 (125)	5450 ± 1110 (23)	0.015
Weight 6 h after admission (g)	6235 ± 1280 (125)	5565 ± 1140 (23)	0.014
Weight gain (%)	2.72 ± 2.29 (125)	2.09 ± 2.25 (23)	0.196
Height (cm)	68.9 ± 6.2 (125)	68.2 ± 6.3 (23)	0.558
Weight-for-age (% NCHS)	58.1 ± 9.0 (125)	54.8 ± 9.8 (23)	0.073
Weight-for-height (% NCHS)	75.4 ± 7.1 (125)	70.4 ± 1.1 (23)	0.033
Duration of diarrhoea before admission (days)	2.8 ± 1.2 (125)	3.0 ± 1.5 (23)	0.301
Number of stools per 24 h before admission	7.8 ± 4.3 (125)	8.6 ± 3.8 (23)	0.215
Number of vomits before admission	3.7 ± 2.2 (65)	3.7 ± 2.2 (11)	0.291
Haematocrit (%)	35.5 ± 5.9 (125)	37.0 ± 6.7 (23)	0.416
Plasma Na (mEq/l)	122.7 ± 12.5 (111)	121.1 ± 13.7 (21)	0.242
Plasma K (mEq/l)	3.2 ± 1.0 (110)	2.8 ± 0.9 (21)	0.061
Total plasma proteins (g/l)	51.9 ± 10.6 (121)	45.1 ± 10.5 (23)	0.013
Plasma specific gravity (g/100 ml)	1.066 ± 0.011 (112)	1.058 ± 0.011 (22)	0.017
Reducing sugars in the stools (g/24 h)	8 ± 12 (103)	18 ± 19 (21)	0.983
	Survived *% (n)*	*Died* *% (n)*	*P*
Female	35 (125)	65 (23)	0.007
Breast-feeding			
Before diarrhoea	66 (125)	39 (23)	0.013
24 h before admission	62 (125)	30 (23)	0.066
Moderate or severe dehydration	70 (125)	91 (23)	0.037
Fever before admission	56 (125)	61 (23)	0.838
Vomiting before admission	44 (125)	48 (23)	0.912

Table 4. Odds ratio of different risk factors associated with death obtained by univariate analysis

Risk factor	*Category (n)*	*Deaths (%)*	*P*	*Odds ratio* *Mean (95% CI)*
Sex	Male (89)[a]	9	0.007	1
	Female (59)	25		3.5 (1.4–8.9)
Breast-feeding	Yes (84)[a]	8	0.006	1
	No (64)	25		3.7 (1.4–9.6)
Dehydration	Mild (39)[a]	5	0.037	1
	Moderate or severe (109)	19		4.4 (1.0–20.0)
Days of diarrhoea before admission	≤3 (100)[a]	11	0.028	1
	>3 (48)	25		2.7 (1.1–6.7)
Weight-for-height (% NCHS)	≤66.6 (23)[a]	39	0.001	1
	>66.6 (125)	11		0.20 (0.07–0.54)
Plasma specific gravity	≤1.053 (21)[a]	38	0.004	1
	>1.053 (113)	12		0.23 (0.08–0.66)
Total plasma proteins (g/l)	≤40 (23)[a]	35	0.007	1
	>40 (121)	12		0.27 (0.10–0.74)

[a]Baseline category.

When including the five deaths which occurred before discharge, but after diarrhoea cessation, the same risk factors were present with similar odds ratios (female sex, absence of breast-feeding, low weight or weight-for-height, moderate or severe dehydration, low plasma protein level and specific gravity). Moreover, a low weight-for-age (<50% of NCHS median) and a low sodium plasma level (<124 mEq/l) appeared to reach significance with odds ratios of 3.8 (95% CI: 1.5–10.0) and 2.7 (95% CI: 1.1–6.7), respectively, whereas the corresponding results were borderline when considering only the deaths during diarrhoeal disease. In the multivariate analysis, the same high risk group was detected, namely non-breast-fed females (eight deaths out of nine) in comparison to the other children (20 deaths among 139). The low risk group was also borderline significant (P = 0.052), with four deaths among 54 breast-fed males.

Discussion

This prospective study showed that, in dehydrated malnourished children treated in a well-defined standardized way, non-breast-fed girls with a low weight-for-height have an especially high risk of dying, even in a hospital setting. Although the purpose of our study was to look for risk factors of dying during diarrhoeal disease, the same high risk group was found when taking into account deaths occurring just after diarrhoea cessation. Selection bias in our sample seems unlikely since only the first two children fulfilling inclusion criteria were selected every day.

Previous hospital studies in Rwanda and India already showed that breast-feeding was associated with better child survival (Lepage, Mungakazi & Hennart, 1981; Sadchev *et al.*, 1991*a*). The study in India also showed that the protective effect of breast-feeding was stronger among severely malnourished children (Sadchev *et al.*, 1991*b*). A selective effect of breast-feeding on survival of severely malnourished children has also been observed in two community studies from rural Bangladesh (Briend, Wojtyniak & Rowland, 1988; Briend & Bari, 1989). Female sex was mentioned as a risk factor in a previous hospital study from Senegal, but this factor was no more significant in multivariate analysis (Beau *et al.*, 1987).

In this study, the degree of dehydration assessed clinically or estimated with plasma specific gravity was not significantly related to the risk of dying in multivariate analysis. Lack of association between the degree of dehydration and the risk of dying in multivariate analysis was already reported in other hospital studies (Briend *et al.*, 1986; Sadchev *et al.*, 1991*b*). Hyponatraemia, however, was found to be significantly related to the risk of dying in multivariate analysis in a previous study from Jamaica (Garrow & Pike, 1967).

The mechanism underlying the selective effect of breast-feeding on the survival of severely malnourished children with diarrhoea is poorly understood. Several hypotheses are plausible. Quality of maternal care may have been better in the breast-fed group, although it seems unlikely that this factor may explain the large mortality difference observed in this hospital study. All children, including those who were not breast-fed, were taken care of by their own mother. Breast milk contains anti-infective factors such as lysozyme, lactoferrin and secretory IgA which may limit the severity of invasive diarrhoeas (Reif & Lebenthal, 1993). In Bangladesh, a case–control study showed that in shigellosis, signs of severity were less frequent among breast-fed children throughout the first 3 years of life (Clemens *et al.*, 1986). Breast milk also contains several known growth factors: epithelial growth factors (EGF), nerve growth factors (NGF), transforming growth factors (TGF) and insulin growth factor, which may have an effect on mucosal repair (Reif & Lebenthal, 1993). Finally, breast milk has a low solute load (Ziegler & Fomon, 1989) and may prevent excessive sodium retention when given in addition to ORS solution and diluting its mineral content. Sodium concentration of the WHO-recommended solution may be too high when given to severely malnourished children (Viteri, 1991; Waterlow, 1992; Briend & Golden, 1993). Among the 23 children who died, seven had signs of respiratory distress which may well have been related to circulatory overload. Weight gain of children who died, however, was lower than in those who survived, which is not in favour of excessive water and sodium retention as a cause of death. Moreover, breast-milk sodium concentration (6 mEq/l) may be insufficient to prevent hyponatraemia (Kingston, 1973).

Determining the mechanisms through which breast milk improves survival may help to design treatment protocols to reduce mortality in non-breast-fed infants. In the meantime, continuation of breast-feeding is the most important measure for improving survival of malnourished children with diarrhoea.

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