PAPERS AND SHORT REPORTS

Risk factors for death in complicated diarrhoea of children

AZIZ R SAMADI, AMINUL I CHOWDHURY, MOHAMMAD I HUQ, NIGAR S SHAHID

Abstract

A total of 1330 children with complicated diarrhoea who were admitted to the general ward of the International Centre for Diarrhoeal Diseases Research, Bangladesh Health Complex, during 1979 were examined. The risk of death by complication of diarrhoea, aetiology, age, and nutritional state was analysed by a logit regression model. Serum sodium concentration and coma were found to be significant predictors of death, death being related directly to coma and inversely to serum sodium concentration. An earlier study had shown that the incidence of hyponatraemia was directly related to the degree of malnutrition, but the results of logit regression analysis did not show the nutritional state to be a predictor of death. Owing to lack of data, however, serum albumin concentration could not be taken as a variable in the logit regression analysis. To determine the relation of serum albumin concentration to hyponatraemia and the cause of death in hyponatraemia further prospective studies would be necessary.

Introduction

Diarrhoeal disease is a leading cause of death among children in developing countries, and most deaths are due to loss of fluids and electrolytes.¹ The interaction between malnutrition and diarrhoea is well known.² In areas where malnutrition is prevalent diarrhoeal disease of diverse aetiology is common. In malnourished children with diarrhoea there is a tendency towards serious complications and increased mortality.³ In an earlier study we found a strong relation between nutritional state and serum sodium concentration, the sodium concentration

being indirectly related to the degree of malnutrition.⁴ We also observed that the incidence of hyponatraemia increased with age. Death was related to serum sodium concentration rather than to age or nutritional state.⁴ The risk of death from complications of diarrhoea as well as from various aetiological agents has not been thoroughly studied previously. This paper presents the results of a logit regression analysis of deaths of children with diarrhoea by complication, aetiology, age, nutritional state, and serum sodium concentration.

Patients and methods

We studied 1330 children aged under 3 who were admitted to the general ward of this health complex in 1979. A detailed description of the children and procedures has been reported previously.⁴ On admission a medical history was obtained from the child's attendant and physical examination performed. Blood for measurement of electrolyte concentrations was taken from all children; blood for measurement of glucose concentrations was obtained only from those suspected clinically of having hypoglycaemia. Microscopy of stools and culture for *Vibrio*, *Shigella*, and *Salmonella* were routinely done by standard methods⁵ along with other routine examinations. Other aetiological investigations were not conducted routinely, but a parallel aetiological study at this hospital from December 1979 to November 1980 showed that among children aged under 3 who visited the health complex Dhaka rotavirus and enterotoxigenic *Escherichia coli* accounted for 30% and 21% of cases, respectively.⁶

Complicated diarrhoea was defined as diarrhoea associated with one or more of the following conditions: chest infection (pneumonia confirmed by x ray film or clinical syndromes such as bronchitis and tracheitis); metabolic acidosis (serum bicarbonate concentration < 15 mmol(mEq)/l); hyponatraemia (serum sodium concentration < 130 mmol(mEq)/l); hypernatraemia (serum sodium concentration > 150 mmol/l); hypokalaemia (serum potassium concentration < 3.5 mmol(mEq)/l); hyperkalaemia (serum potassium concentration > 5.5 mmol/l); hypoglycaemia (serum glucose concentration < 2.2 mmol/l (39.6 mg/100 ml)); coma; and non-specific convulsions and malnutrition (assessment of nutritional state described previously⁴). Serum electrolyte concentrations were measured by I-L flame photometer,⁷ and serum glucose concentration was determined by the Somogyii method. All children with mild to severe dehydration were given intravenous acetate solution for initial rehydration,⁴ followed by either physiological saline or half strength saline plus 5% dextrose, depending on serum sodium concentrations.

The differences in case fatality from complications of diarrhoea by serum sodium concentration (isonatraemia, hyponatraemia, and

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hypernatraemia) were tested using χ^2 statistics. In testing by χ^2 when the child did not die 0.5 was added in all respective cells. The prediction of death (dependent variable) by each independent variable (complication and aetiology) was obtained by multiple linear regression. The overall validity of the model was tested by the F test. To test the significance of each independent variable a two tailed t test was applied. The variables that were significant at the 0.10 confidence level in the multiple linear regression analysis were then analysed by a logit regression model (global model).⁸ Age and nutritional state, because of their significant relation with the incidence of hyponatraemia,⁴ were also included in the logit regression model. Age, nutritional state, serum potassium concentration, and serum sodium concentration were run as continuous variables in the logit regression analysis, by which we estimated the independent effect of the correlates of all variables for death using the maximum likelihood method of Duncan-Walker.⁹ The significant variables (at the 0.05 confidence level) were then analysed in a logit reduced model. The data were analysed by an IBM System 34 computer.

Results

Overall case fatality was 5% (66/1330). The case fatality from aetiological agents detected was: *Shigella* 6.6% (11/167), *V. cholerae* 01 14.3% (6/42), non-agglutinating *V. cholerae* 0% (0/6), and *Salmonella* 16.6% (1/6). Case fatality among children in whom the aetiology was unknown was 4.3% (48/1118).

Case fatality by serum sodium concentration was 10.1% in children with hyponatraemia, 3.8% in those with isonatremia, and 1.2% in those with hypernatraemia ($\chi^2=21.00$, $df=2$, $p<0.0001$). Deaths associated with chest infection, metabolic acidosis, and hypokalaemia were significantly more common in children with hyponatraemia than those with isonatremia and hypernatraemia ($\chi^2=10.03$, $df=2$, $p<0.01$; $\chi^2=8.21$, $df=2$, $p<0.02$; and $\chi^2=16.03$, $df=2$, $p<0.001$, respectively) (table I).

Table II shows the probability of death from complications of diarrhoea and aetiologies by the multiple linear regression method. Hyponatraemia, hyperkalaemia, coma, and hypoglycaemia were significant predictors of death at the 0.10 confidence level ($p<0.005$,

TABLE III—Logit regression coefficients with standard error, statistical test, and adjusted p of effect of complications of diarrhoea, age, and nutritional state on death (global model)

Variables	Coefficients	Standard error	t ratio	Adjusted p
Constant	7.8428	2.2775	3.44**	
Serum sodium	-0.0770	0.0166	-4.64***	0.0184
Coma	1.0273	0.4909	2.09*	0.0404
Serum potassium	0.0986	0.0863	1.14	0.0395
Hypoglycaemia	-0.8724	0.8314	1.05	0.0392
Age (months)	-0.0030	0.0121	-0.25	0.0390
Nutritional state	-0.0010	0.0056	0.18	0.0380

Likelihood ratio statistic $\chi^2=35.85$, $df=6$, $p<0.0001$.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

TABLE IV—Logit regression coefficients with standard error, statistical test, and adjusted p of effect of serum sodium concentration and coma on death (reduced model)

Variables	Coefficients	Standard error	t ratio	Adjusted p
Constant	7.8578	2.1444	3.66**	
Serum sodium	-0.0816	0.0163	-5.00***	0.0175
Coma	1.0236	0.4828	2.12*	0.0998

Likelihood ratio statistic $\chi^2=33.33$, $df=2$, $p<0.0001$.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

$p<0.01$, $p<0.01$, and $p<0.10$, respectively). The overall validity of the model was significant ($F=4.07$, $df=14$ and 1315 , $p<0.0001$).

The predictors of death by complication, age, and nutritional state were shown by a global model (table III). The overall validity of the model was significant (likelihood ratio statistic $\chi^2=35.85$, $df=6$, $p<0.0001$). Among these variables serum sodium concentration and coma were the most significant predictors of death: death was related directly to coma and inversely to serum sodium concentration (t ratio=2.09, $p<0.05$, and t ratio=-4.64, $p<0.001$, respectively).

The predictors of mortality from serum sodium concentration

TABLE I—Death from complications of diarrhoea by serum sodium concentration

Variables	Serum sodium (mmol(mEq)/l)						2 × kχ ² (p value)*
	130-150 (mean (SD) 137.2 (4.8)) (n = 969)		<130 (mean (SD) 124.6 (4.2)) (n = 276)		>150 (mean (SD) 156.1 (6.4)) (n = 85)		
	No of cases	No (%) of deaths	No of cases	No (%) of deaths	No of cases	No (%) of deaths	
Chest infection	542	19 (3.5)	143	14 (9.8)	33	1 (3.0)	10.13 (p < 0.01)
Serum bicarbonate < 15 mmol(mEq)/l	266	13 (4.9)	92	11 (11.9)	40		8.21 (p < 0.02)
Serum potassium < 3.5 mmol(mEq)/l	468	16 (3.4)	134	15 (11.2)	51		16.03 (p < 0.001)
Serum potassium > 5.5 mmol(mEq)/l	40	7 (17.5)	25	5 (20.0)	3		0.20 (NS)
Hypoglycaemia	137	8 (5.8)	42	3 (7.1)	16	1 (6.2)	0.09 (NS)
Convulsions	38	1 (2.6)	23	2 (8.7)	6	1 (16.6)	2.28 (NS)
Coma	20	5 (25.0)	16	1 (6.2)	1		1.91 (NS)
Total		37 (3.8)		28 (10.1)		1 (1.2)	21.00 (p < 0.0001)

* $df=2$.

TABLE II—Probability of death from complications of diarrhoea and aetiology (by multiple linear regression analysis)

Variables	Regression coefficients	Standard error	t ratio	p value	χ^2
Constant	-0.1062				
Chest infection	-0.0028	0.0119	-0.2376	0.810	
Serum bicarbonate <15 mmol(mEq)/l	0.0060	0.0132	0.4565	0.650	
Serum sodium <130 mmol(mEq)/l	0.0430	0.0152	2.8395	0.004*	
Serum sodium >150 mmol(mEq)/l	-0.0298	0.0245	-1.2145	0.220	
Serum potassium <3.5 mmol(mEq)/l	0.0116	0.0123	0.9433	0.340	
Serum potassium >5.5 mmol(mEq)/l	-0.1012	0.0240	-4.2255	0.001*	
Hypoglycaemia	-0.1033	0.0636	-1.6014	0.099*	
Coma	0.0938	0.0361	2.5946	0.009*	
Convulsions	-0.0074	0.0277	-0.2686	0.788	
<i>V. cholerae</i>	0.0917	0.2168	0.4232	0.672	
Non-agglutinating <i>V. cholerae</i>	-0.0317	0.2312	-0.1373	0.891	
<i>Shigella</i>	0.0313	0.2147	0.1457	0.884	
<i>Salmonella</i>	0.1254	0.2315	0.5437	0.586	
Unknown	0.0197	0.2141	0.0920	0.926	

$\chi^2_{df}=1315$.

*Significant at 0.10 confidence level.

F test = 4.07 ($df=14$ and 1315), $p<0.0001$.

and coma were shown by a reduced model (table IV). The overall validity of the model was significant (likelihood ratio statistic $\chi^2=33.33$, $df=2$, $p<0.0001$). Both serum sodium concentration and coma were significant predictors of death: death was related directly to coma and inversely to serum sodium concentration (t ratio=2.12, $p<0.05$, and t ratio=-5.00, $p<0.001$, respectively). The difference in likelihood ratio statistic χ^2 between the global and reduced models was not significant ($35.85-33.33=2.52$, $df=6-2$, $p>0.05$). This implies that the combined effect of all the factors omitted from the global model to produce the reduced model was not significant.

Discussion

The risk of death from chest infection, metabolic acidosis, and hypokalaemia was significantly higher among children with hyponatraemia than those with isonatremia or hypernatraemia. As some of these children had more than one

complication it might be difficult to conclude which was the most significant risk factor for death. None the less, overall case fatality rate was highest among children with hyponatraemia.

The multiple linear regression model showed that deaths associated with hyponatraemia, hyperkalaemia, and hypoglycaemia were significant at the 0.10 confidence level, but the effect of confounding factors could not be measured.

In the logit regression model, which measures the effect of confounding factors, all the variables except serum sodium concentration and coma lost their effects. This observation that death was inversely related to serum sodium concentration supports our earlier findings that hyponatraemia is the most significant risk factor among children with complicated diarrhoea in Bangladesh.⁴ We reported earlier that the incidence of hyponatraemia was directly related to the degree of malnutrition, but the results of the logit regression analysis did not show that malnutrition was a significant predictor of death. The reason for the direct relation of the incidence of hyponatraemia to the degree of malnutrition might be that serum albumin concentration carries a negative charge and is largely responsible for the normal anion gap by holding serum sodium in the intravascular space.^{10 11} Although nutritional state was not found to be a predictor of death, the serum albumin concentration in these children was not run as a variable in the logit regression model owing to lack of data. None the less, hyponatraemia remained a significant predictor of death, though we do not have any satisfactory explanation for this. The direct relation between the incidence of hyponatraemia and the degree of malnutrition necessitates further, prospective studies to assess the effect of serum albumin concentration on the physiopathology of hyponatraemia.

The finding of coma as a predictor of death was not expected. As postmortem examinations were not performed we are

unable to discuss the cause of the coma and its relation to death.

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References

- 1 Puffer RR, Serrano CV. *Patterns of mortality in childhood: report of the inter-American investigation of mortality in childhood*. Washington DC: Pan American Health Organisation, 1973. (Scientific publication No 262.)
- 2 Scrimshaw NS, Tayler CE, Gordon IE. *Interaction of infection and nutrition*. Geneva: WHO, 1968. (WHO Monograph Series No 57.)
- 3 James JW. Longitudinal study of the morbidity of diarrhoeal and respiratory infections in malnourished children. *Am J Clin Nutr* 1972;25:690-4.
- 4 Samadi AR, Wahed MA, Islam MR, Ahmed SM. Consequences of hyponatraemia and hypernatraemia in children with acute diarrhoea in Bangladesh. *Br Med J* 1983;286:671-3.
- 5 Edwards PR, Ewing WH. *Identification of enterobacteriaceae*. 3rd ed. Minneapolis: Burgess, 1972.
- 6 Stoll BJ, Glass IR, Huq MI, Khan MU, Haldt JE, Banu H. Surveillance of patients attending a diarrhoeal disease hospital in Bangladesh. *Br Med J* 1982;285:1186-8.
- 7 Haven GT, Haven MC. Serum sodium measurement by manual and on-line dilution. *Clin Chem* 1973;19:791.
- 8 Haberman SH, Duncan DB. *Analysis of quantitative data*. Vol 1. New York: Academic Press, 1979.
- 9 Walker SH, Duncan DB. Estimation of the probability of an event as a function of several independent variables. *Biometrika* 1967;54:167-78.
- 10 Emmet M, Narins RG. Clinical use of the anion gap. *Medicine (Baltimore)* 1977;56:38.
- 11 Oh MS, Carrol HJ. The anion gap. *N Engl J Med* 1977;297:814.

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Progesterone and the premenstrual syndrome: a double blind crossover trial

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Abstract

A double blind, randomised, crossover trial of oral micronised progesterone (two months) and placebo (two months) was conducted to determine whether progesterone alleviated premenstrual complaints. Twenty three women were interviewed premenstrually before treatment and in each month of treatment.

They completed Moos's menstrual distress questionnaire, Beck et al's depression inventory, Spielberger et al's state anxiety inventory, the mood adjective checklist, and a daily symptom record. Analyses of data found an overall beneficial effect of being treated for all variables except restlessness, positive moods, and interest in sex. Maximum improvement occurred in the first month of treatment with progesterone. Nevertheless, an appreciably beneficial effect of progesterone over placebo for mood and some physical symptoms was identifiable after both one and two months of treatment.

Further studies are needed to determine the optimum duration of treatment.

Introduction

Most women are aware of changes in their mood, behaviour, and body during the menstrual cycle. In some women these changes are severe enough to lead to presentation with complaints of premenstrual tension. Although a specific syndrome of premenstrual tension was described by Frank in 1931,¹ later authors added greatly to the symptomatology and length of

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