incidences of connective tissue diseases; and participated in the study design, data interpretation, and editing of the paper. LH discussed core ideas and participated in initiation of the study, formulation of the primary study hypothesis, protocol design, data interpretation, and editing of the paper. JDB discussed core ideas; made suggestions about analyses; and participated in data interpretation and editing of the paper. H-OA initiated the research and participated in the protocol design, data interpretation and writing of the paper.

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Single dose vitamin A treatment in acute shigellosis in Bangladeshi children: randomised double blind controlled trial

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Abstract

Objective: To evaluate the efficacy of a single large oral dose of vitamin A in treating acute shigellosis in children in Bangladesh.

Design: Randomised double blind controlled clinical trial.

Setting: Dhaka Hospital, International Centre for Diarrhoeal Disease Research, Bangladesh.

Subjects: 83 children aged 1-7 years with bacteriologically proved shigellosis but no clinical signs of vitamin A deficiency; 42 were randomised to treatment with vitamin A and 41 formed a control group.

Intervention: Children were given a single oral dose of 200 000 IU of vitamin A plus 25 IU vitamin E or a control preparation of 25 IU vitamin E.

Main outcome measures: Clinical cure on study day 5 and bacteriological cure.

Results: Baseline characteristics of the subjects in the two treatment groups were similar. Significantly more children in the vitamin A group than in the control group achieved clinical cure (19/42 (45%) *v* 8/14 (20%); $\chi^2 = 5.14$, 1 df, $P = 0.02$; risk ratio = 0.68 (95% confidence interval: 0.50 to 0.93)). When cure was determined bacteriologically, the groups had similar rates (16/42 (38%) *v* 16/41 (39%); $\chi^2 = 0.02$, 1 df, $P = 0.89$; risk ratio = 0.98 (0.70 to 1.39)).

Conclusions: Vitamin A reduces the severity of acute shigellosis in children living in areas where vitamin A deficiency is a major public health problem.

Introduction

Shigellosis remains one of the most severe enteric infections affecting children in developing countries, including Bangladesh.[1 2] It results in the frequent passage of small, bloody mucoid stools; abdominal cramps; and tenesmus caused by ulceration of the colonic epithelium.[3–6] In addition to high mortality from shigellosis, the protein losing enteropathy is a serious complication that probably contributes to the malnutrition and growth stunting associated with the disease.[7–11]

Reports that vitamin A supplementation reduces childhood mortality from diarrhoeal diseases and measles related diarrhoea have been published.[12–17] Other studies have found reduced disease severity and lower morbidity in patients with diarrhoea treated with vitamin A.[18–20] These findings are important for developing countries such as Bangladesh, where shigellosis is one of the most important contributors to childhood morbidity and mortality. Although appropriate antibiotic treatment shortens the course of shigellosis, morbidity and mortality are still high.[21–23] Reports of beneficial effects of vitamin A supplementa-

tion on diarrhoea and evidence that vitamin A has a physiological role in maintaining epithelial integrity and in stimulating specific and non-specific immune functions suggest that it may prove an effective adjuvant to antibiotic treatment in shigellosis.[24–31] However, the role of vitamin A in the treatment of acute shigellosis in children has not been evaluated before.

This study aimed to determine whether treatment with vitamin A together with a standard antibiotic would reduce the severity of shigellosis. We carried out a randomised double blind controlled trial in hospital to determine the treatment effect of a large single oral dose of vitamin A in children with proved shigellosis.

Methods

Protocol

The study was organised and conducted at the Dhaka hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh. Altogether 90 subjects were enrolled in the trial during the period September 1992 to December 1994. The study was reviewed and approved by the research review committee and ethics committee of the International Centre for Diarrhoeal Research, Bangladesh. The parents and guardians of all the study children gave written informed consent.

Recruitment and enrolment

Children were eligible for the trial if they were *(a)* aged between 1 and 7 years, *(b)* had no other acute or chronic illnesses, *(c)* presented to the outpatient department because they had been passing bloody mucoid stools (for less than 72 hours), and *(d)* if microscopic examination of stools showed ≥20 pus cells and erythrocytes per high power field and no trophozoites of *Entamoeba histolytica*.

Children were excluded from the trial if *(a)* they had been given antibiotics for the present illness, *(b)* they had received vitamin A during the previous 3 months, *(c)* their weight for age was ≤75% of the national child health statistics growth reference median, *(d)* one of the *Shigella* sp was not isolated from the baseline stool or rectal swab samples, *(e)* subsequent microscopic examination of stools showed trophozoites of *E histolytica*.

The final trial subjects comprised those children in whom infection with *Shigella* spp had been proved by culture of the stool or rectal swab using a standard technique.[32]

Study design and randomisation

A randomised double blind controlled design was used for this trial. A computer generated randomisation plan with a block size of six was used to assign individual subjects to a vitamin A or a control preparation. A senior member of staff in the clinical sciences division of the International Centre for Diarrhoeal Disease Research, who was not directly involved in recruiting subjects, subject evaluation, or data analysis, created the list of subjects' identification numbers and corresponding treatment assignments. To conceal treatment allocation, this person provided the appropriate identification number and medication from the list when a subject was ready to be enrolled.

Study intervention

At enrolment, subjects were assigned to treatment with a single oral dose of 200 000 IU of water miscible vitamin A in the form of retinyl palmitate plus 25 IU of vitamin E or a control preparation of 25 IU of vitamin E. The treatment and control preparations were identical in colour, taste, flavour, and volume. Both preparations were kept in an amber coloured bottle, and neither the research team nor the children's parents or guardians knew which preparation the bottles contained. To ensure compliance, the trial treatment and control preparations were administered by a research assistant. On no occasion were details of treatment assignment disclosed; the code was broken only after the final analysis.

Evaluation of patients

At enrolment, a medical history and physical examination were completed by a research assistant (physician) and recorded on a standardised form. Before subjects were randomised to treatment group, stool and rectal swab samples were taken for culture of *Shigella* spp, *Salmonella* spp, *Vibrio cholerae* O1, *Plesiomonas shigelloides*, and *Campylobacter jejuni*; a full blood count was done; and serum electrolytes were determined.

Each day fresh stool and rectal swab samples were sent for culture of *Shigella* spp. Physical examinations and symptoms were recorded every 8 hours by research assistants. Stool frequency and consistency, including the presence of blood or mucus, or both, were determined by a nurse who counted and examined soiled diapers and recorded findings immediately on a tally sheet.

Medical care

Each child was given nalidixic acid (55 mg/kg body weight daily, every 6 hours), but after 48 hours the antibiotic was changed if the sensitivity test suggested this was advisable. Children were admitted to hospital for 5 study days after they had been given the trial treatment.

Outcome measures

The primary end points were achievement of clinical cure on study day 5 and of bacteriological cure. Subjects were considered cured clinically if they passed three or fewer formed stools in a day without any visible blood or mucus, were afebrile, and had no abdominal pain or tenderness on that study day. Bacteriological cure was defined as the continuing absence of *Shigella* spp in both stool and rectal swab samples from study day 3 onwards. Stool frequency was defined as the number of stools passed each study day. Stools that could be poured or predominantly contained blood or mucus, or both, were considered liquid stools. Complaints of abdominal pain or the presence of abdominal tenderness and a rectal temperature ≥37.8°C during any 8 hour study period were defined as pain and fever respectively for that study day. Study days were deemed to begin at the time trial treatment had been given.

Estimates of sample size

The pretrial sample size was based on a previous study in which 70% of subjects achieved clinical and bacteriological cure with a standard treatment on study

Baseline characteristics of trial subjects in relation to treatment group

Characteristics	Control group (n=41)	Vitamin A group (n=42)
Median (interquartile range) age (months)	34 (24-50)	33 (19-54)
Mean (SD) body weight (kg)	11 (2)	11 (3)
No (%) boys	26 (63)	19 (45)
Symptoms before enrolment:		
Median (interquartile range) duration (hours)	50 (30-70)	45 (28-62)
Median (interquartile range) stool frequency in previous 24 hours*	24 (15-30)	23 (20-25)
Median (interquartile range) duration of blood in stools (hours)*	32 (22-54)	28 (18-52)
No (%) with fever*	38 (93)	42 (100)
No (%) with abdominal pain/tenderness	36 (88)	36 (86)
No (%) of stool cultures		
Shigella dysenteriae type 1	26 (64)	28 (67)
S flexneri	14 (34)	11 (26)
S sonnei or *S boydii*, or both	1 (2)	3 (7)
Stool microscopy (cells/high power field)		
No (%) with ≥50 pus cells	39 (95)	41 (98)
No (%) with ≥50 erythrocytes	33 (81)	33 (79)

No comparisons were statistically significant.
*Determined by history on the day of enrolment.

day 5.[33] Power and sample size calculations were made by computer program.[34] For this trial to show a relative risk of 1.4 in the vitamin A group compared with the control group in relation to clinical and bacteriological cure, a maximum sample size of 41 was considered necessary for each group, assuming $\alpha = 0.05$ and power = 90%.

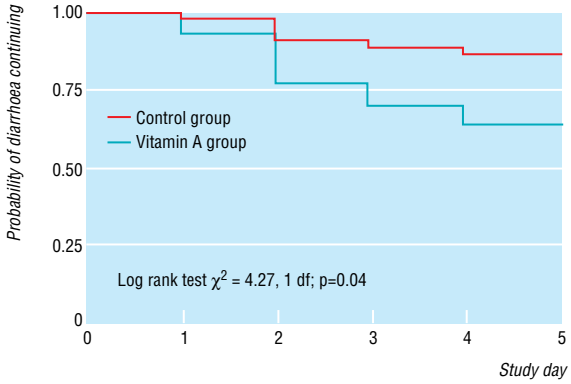
Statistical analysis

The STATA statistical program (release 4.0) was used for data entry and analysis. Continuous variables that were normally distributed were evaluated by Student's *t* tests, and the Wilcoxon rank sum test was used for data with a skewed distribution. Bivariate variables were compared by χ^2 test. Risk ratios and 95% confidence intervals were calculated with the EpiInfo software package (version 6). Kaplan-Meier survival curves and the log rank test were used to evaluate the difference in time taken to achieve a clinical cure in the groups.

Results

Comparability of groups at baseline

Ninety subjects were initially enrolled in the study, but seven were excluded subsequently. Three control subjects were excluded—one developed haemolytic uraemic syndrome and in two *Shigella* spp could not be cultured in the initial stool or rectal swab. Four subjects in the vitamin A group were excluded—in two children *Shigella* spp could not be cultured in the initial stool or rectal swabs, one left hospital against medical advice on study day 2, and one child had *E histolytica* in the stool sample. The final analysis included 83 subjects—42 in the vitamin A group and 41 in the control group. Baseline characteristics of the trial subjects were similar for each of the treatment groups (table).



Time to onset of clinical cure of shigellosis

Analysis of clinical cure

Forty five per cent (19 of 42) of children in the vitamin A group and 20% (8 of 41) in the control group were cured clinically by day 5 ($\chi^2 = 5.14$, 1 df, $P = 0.02$; risk ratio = 0.68 (95% confidence interval 0.50 to 0.93)). Kaplan-Meier survival curves showed a higher rate of clinical cure in the vitamin A group from day 2 (figure). The null hypothesis that the two survival curves are equal was rejected by a log rank test ($\chi^2 = 4.27$, 1 df; $P = 0.04$).

Analysis of bacteriological cure

No significant difference in bacteriological cure between the groups was found. This was achieved by 38% (16 of 42) in the vitamin A group and 39% (16 of 41) in the control group ($\chi^2 = 0.02$, 1 df; $P = 0.93$; risk ratio = 0.98 (0.57 to 1.68)).

Discussion

This is the first published study in which vitamin A has been used as an adjunct to antibiotic treatment in shigellosis. A single oral dose of 200 000 IU of vitamin A accelerated clinical cure in children with shigellosis, and no adverse effects were noted.

Vitamin A might have reduced the severity of shigellosis via two main mechanisms. Firstly, vitamin A is adequately absorbed across the intestinal epithelium, even during episodes of acute diarrhoea, and is probably available to the colonic epithelium almost immediately after absorption.[35–37] The rapid delivery of vitamin A to the affected site in the intestine may have enhanced repair of the micro-ulcers in the gut epithelium. Secondly, animal studies show that a high dose of vitamin A stimulates phagocytosis and cell mediated killing of pathogens. Vitamin A may therefore reduce the severity of shigellosis by stimulating the immune system.[30 31]

Because shigellosis affects epithelial tissues extensively and causes an intense immune response, treatment with vitamin A might be expected to reduce the severity of the disease. Although the exact mechanism by which vitamin A reduces the severity of other diseases is not yet known, it has been suggested that it is related to an improvement in immune function and a rapid regeneration of epithelial tissues.[38 39]

A recent meta-analysis of all the randomised controlled community trials of vitamin A supplementation reported a 39% reduction in mortality from diarrhoeal disease.[40] This reduction did not seem to result from a reduction in the incidence of diarrhoeal diseases so much as from a reduction in the severity of attacks. This finding is consistent with our results.

Trials of vitamin A supplementation in Brazil and Ghana have reported that it reduced the incidence or prevalence of severe diarrhoea.[41 42] Our results are con-

sistent with these findings and suggest that some beneficial effects of vitamin A in the prevention of diarrhoea may be related to its effects in reducing the severity of dysentery due to *Shigella* spp. However, no benefit of vitamin A treatment was found in children with acute watery diarrhoea due to enterotoxigenic *Escherichia coli* or rotavirus.[43] Differences in the pathogenesis and duration of episodes of shigellosis compared with enterotoxigenic *E coli* and rotavirus diarrhoea may explain this variation in the response to treatment with vitamin A. In our study the rate of both clinical and bacteriological cure was lower by day 5 than in the previous studies; this may be explained by the higher resistance of the isolated *Shigella* spp to nalidixic acid (64%) during the trial period.[22 23]

The strengths of our trial include the randomised double blind controlled design; successful concealment of treatment allocation; complete follow up of all trial subjects (except one in each group) for 5 days; and the hospital setting, which allowed us to make accurate assessments of the clinical and bacteriological variables. Furthermore, the similarity of treatment groups in terms of baseline characteristics shows that random allocation of subjects to treatment groups was effective.

Conclusion

These results indicate that treatment with a single oral dose of 200 000 IU vitamin A along with a standard antibiotic reduces the severity of acute shigellosis in children aged more that 1 year. However, vitamin A supplementation does not accelerate bacteriological cure. As with other infectious diseases, shigellosis probably increases the requirement for vitamin A.[44 45] Among children in countries such as Bangladesh, where vitamin A deficiency is a major public health problem and shigellosis is endemic, vitamin A supplementation should be added to the standard treatment for acute shigellosis.[46] This treatment would help to hasten clinical cure and probably restore the vitamin A status. A reduction in the severity of shigellosis will reduce the level of childhood morbidity and mortality in these countries.

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Contributors: SH, the principal investigator, initiated the study hypotheses, designed the protocol, and did statistical analysis under the supervision of DM and MD. SS and IK participated in protocol design and medical care of subjects. RB recruited subjects, documented data, and entered data into the computer and also gave medical care to subjects. MD, DM, and GF helped in the interpretation of data. The paper was written jointly by SH, MD, and GF. Guarantors: SH, DM.

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Conflict of interest: None.

Key messages

- A single oral dose of 200 000 IU vitamin A acts as an adjunct in the treatment of acute shigellosis among the children in geographical areas where vitamin A deficiency is a major public health problem
- Vitamin A supplementation hastens clinical cure in acute shigellosis
- Vitamin A supplementation during acute shigellosis has no effect on bacteriological clearance
- Vitamin A may reduce the severity of acute shigellosis by promoting repair of the colonic mucosa and stimulating the immune system

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Mortality from overdose among injecting drug users recently released from prison: database linkage study

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Abstract

Objective: To assess whether injecting drug users have a higher than usual risk of death from overdose in the 2 weeks after release from prison.

Design: Soundex coding of surnames and information on date of birth were used to link entry and release dates from the local prison between 1983 and 1994 with clinical data from Edinburgh City Hospital's cohort of male injecting drug users who are infected with HIV.

Setting: Edinburgh City Hospital and Edinburgh Prison.

Subjects: 316/332 male injecting drug users infected with HIV in the City Hospital HIV cohort; 16 were excluded because they were enrolled after developing AIDS or because their precise date of death was not available.

Main outcome measure: Relative risk of dying from overdose before developing AIDS and relative risk of dying of all causes before developing AIDS during the 2 weeks after release from prison; this was compared with relative risks of death during other time at liberty.

Results: 238/316 (75%) injecting drug users served time in the prison between 1983 and 1994. 33 out of 316 injecting drug users who were infected with HIV died before developing AIDS during 517 177 days at risk. 20 of these men died of an overdose; 6 of these deaths occurred within 2 weeks of release during 5903 days at risk. Death rates from overdose before the development of AIDS were 1.02/1000 days during the 2 weeks after release (recently released) and 0.029/1000 days during other times of liberty. The relative risk of death from overdose became 7.7 (1.5 to 39.1) after temporal matching (when the comparison was limited to the first 2 weeks after release *v* the next 10 weeks). The crude relative risk in an analysis combining stratified prison term and the 2 weeks after release was 4.5 (1.7 to 11.7) for death from overdose. After temporal matching these risks became 1.8 (0.4 to 9.2).

Conclusion: Prisons should evaluate interventions to reduce the risk of death from overdose after release.

Introduction

The risk of death from overdose may be greater in injecting drug users who resume drug use after a period of abstinence during which their tolerance may have declined.[1] Imprisonment is an enforced period of abstinence from, or may lead to a radical reduction in, drug use.[2] We investigated the risk of death from overdose among male injecting drug users in the Edinburgh City Hospital HIV cohort[3] in the 2 weeks after release from the local prison and compared the risk with that of death from overdose at other times.

Subjects and methods

An alphabetical and soundex coded list of 704 names and dates of birth was compiled by RPB. The list included all male patients infected with HIV in the Edinburgh City Hospital cohort (injecting drug users who used mainly heroin, drug users who did not inject drugs, and patients who did not use drugs) and male