

Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovine colostrum

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Background. Oral ingestion of immunoglobulins in humans has been shown to be effective as prophylaxis against enteric infections. However, its therapeutic effect in children with infectious diarrhea has hitherto not been proven. We treated children with rotavirus diarrhea with immunoglobulins extracted from immunized bovine colostrum (IIBC) containing high titers of antibodies against four rotavirus serotypes.

Methods. In this double blind placebo-controlled trial, 80 children with rotavirus diarrhea were randomly assigned to receive orally either 10 g of IIBC (containing 3.6 g of antirotavirus antibodies) daily for 4 days or the same amount of a placebo preparation. The daily stool output (grams/kg/day), intake of oral rehydration solution (ml/kg/day), stool frequency (number of stools/day) and presence of rotavirus in stool were monitored for the 4 days during treatment.

Results. Children who received IIBC had significantly less daily and total stool output and stool frequency and required a smaller amount of oral rehydration solution than did children who received placebo ($P < 0.05$). Clearance of rotavirus from the stool was also earlier in the IIBC group compared with the placebo group (mean day, 1.5 vs. 2.9, $P < 0.001$). No adverse reactions from the colostrum treatment were observed.

Conclusions. Treatment with antirotavirus immunoglobulin of bovine colostrum origin is effective in the management of children with acute rotavirus diarrhea.

INTRODUCTION

Rotavirus is a leading viral enteropathogen responsible for 11 to 71% of diarrhea in infants and children worldwide and causes close to 1 million deaths annually.¹ In the United States alone rotavirus is associated with 3% of all hospitalizations of children younger than 5 years old, resulting in medical and indirect cost in excess of US\$1 billion each year.² Although oral rehydration solution (ORS) has substantially reduced the mortality from dehydration, it has little or no effect on the course of diarrhea or nutritional morbidity. Recent achievements in vaccine development are promising, but even if an effective vaccine becomes available, its use may be limited by financial constraints in developing countries. Moreover its foreseeable efficacy in children with malnutrition and concomitant immunodeficiency is questionable.

The prophylactic effect of breast milk antirotavirus IgA antibody has been suggested to be of some importance³ but has been demonstrated in only a few studies.^{4, 5} However, its role in mitigating acute infection has been questioned.⁶ Beneficial prophylactic^{7, 8} and therapeutic⁹ effects have also been observed with orally administered IgG preparations in rotavirus gastroenteritis. The use of human gamma-globulin preparations, however, is limited by the risk of viral contamination and high production and storage costs of such preparations. Therefore, there is interest in identifying an alternative source of antibodies which is inexpensive, easy to produce and safe.

Colostrum from nonimmunized cows contains antibodies against enteric pathogens, but the titer of antibodies is too low to provide prophylaxis against infections.^{10, 11} This limitation has been overcome by using antibodies in hyperimmunized bovine colostrum (HBC) after vaccination of pregnant cows against specific pathogens. Hyperimmune bovine colostrum against all four human serotype of rotavirus has been effectively used to induce prophylaxis against rotavirus diarrhea in hospitalized children^{12, 13} and in children living in orphanages,¹⁴ yet mass prophylaxis with HBC has

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logistic and economic limitations, particularly in developing countries. Using crude HBC, Mitra et al.¹⁵ demonstrated less stool output in children with rotavirus diarrhea. The use of this product is limited by the requirement to feed a large volume (300 ml/day) to achieve clinical benefit. In this study we present findings of the first double blind placebo-controlled trial with lyophilized antirotavirus immunoglobulin from colostrum of immunized cows to treat children with severe rotavirus diarrhea.

METHODS

Study population. Male infants and children (weight for age, >60% of National Centre for Health Statistics), ages 4 to 24 months with a history of acute watery diarrhea (passage of four or more loose or watery stool in a 24-h period) for <48 h with some dehydration, attending at the Clinical Research and Service Centre of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) were enrolled between March, 1995, and December, 1996. Informed consent from parents or guardians was obtained before enrollment to the study. The children were kept in the clinical research ward for 4 h (observation period) for screening for rotavirus and for oral rehydration as recommended by WHO. Stool samples were tested for cholera by dark field microscopic examination and for rotavirus antigen by enzyme-linked immunosorbent assay (ELISA).¹⁶ Children with a positive ELISA test, with a negative dark field examination and who had stool rate >20 ml/kg during the observation period were eligible for the study. Any child with systemic infections, marasmus or kwashiorkor or a negative ELISA for rotavirus was excluded.

The study was approved by Ethical and Research Review Committees of the ICDDR, B.

Treatment protocol. After inclusion children were randomly assigned to either immunoglobulin from immunized bovine colostrum (IIBC) or a milk powder (placebo) (Imulin[®]). Both IIBC and placebo were identical in appearance, color and taste and were kept in identical appearing bottles before dispensing. The children were fed 10 g of IIBC or placebo dissolved in 20 ml of water in four divided doses for 4 days. The feeding was performed under direct supervision of a nurse for 10 min.

The children were maintained on a "cholera cot," and pediatric urine collection bags were applied to collect urine without contamination from stools. Ongoing stool loss was replaced by WHO-ORS. Breast-fed children continued to have their mother's milk in addition to milk formula unless exclusively breast-fed. Stool and urine output, intake of food and ORS were carefully measured using a balance (1 g sensitivity). Stool frequency was also recorded.

Laboratory tests. At the time of admission rectal

swab samples were cultured for *Salmonella* sp., *Shigella* sp. and *Vibrio cholerae*. Stools were also examined daily for 4 days for rotavirus antigen by ELISA test. Complete blood count and serum electrolytes were also performed.

Endpoints. The children remained in the hospital until cessation of diarrhea which was defined as the last watery or loose stool before the passage of two consecutive soft or formed stools or the occurrence of 12 h without stool.

Production of IIBC. The IIBC was produced by vaccination of pregnant cows in a Swiss dairy farm with human strains of rotavirus, i.e. WA, RV3, RV5 and ST3, representing serotypes 1 to 4, respectively. The preparation and the antiviral activity of the concentrate is described in detail elsewhere.¹⁰ In brief the concentrate was prepared from colostrum by purification, pasteurization and removal of milk fat, casein, lactose and mineral salts. The product was then sterile filtered, and the resulting whey protein solution was freeze-dried. The antibody concentration of the powder was 36 g/100 g of dried antirotavirus milk concentrate. The neutralization titers as measured in type neutralization test against the serotype were as follows: serotype 1, 7500; serotype 2, 2000; serotype 3, 4500; and serotype 4, 4500. The compositions of the immunoglobulin were 75% IgG1, 3% IgG2, 17% IgA and 6% IgM.¹⁰ The placebo was prepared from milk of nonimmunized cows (Imulin[®]; New Zealand Dairy Board, Wellington, New Zealand) (lactose of 22%) and contained very insignificant amount of immunoglobulin (0.2 g/dl). Both the IIBC and placebo were well-preserved in room temperature.

Outcome measures. The major outcome variables were stool rate (grams/kg/day), intake of ORS (ml/kg/day), stool frequency, number of days required for rotavirus ELISA-negative stool and duration of diarrhea after initiation of therapy.

Randomization. Randomization was controlled by a pharmacist holding the IIBC and placebo. A master randomization chart was prepared with the use of random permuted blocks. Both the IIBC and the Imulin[®] powder were dispensed in identical bottles and serially numbered corresponding to the serial number of patients enrolled in the study. The codes of IIBC and placebo were known to the pharmacist, and identification of study and control groups was broken after the acquisition of data including analysis was completed.

Sample size calculation. The sample size was calculated based on three outcome variables, e.g. duration of diarrhea, stool rate and virus excretion in stools. The mean duration of diarrhea, mean total stool volume and mean duration of viral excretion of untreated rotavirus children after admission were 57 h,¹⁷ 216 g/kg¹⁸ and 122 h, respectively.¹¹ To ensure a 30% or

greater reduction of all the outcome variables by treating with IIBC, the sample size needed in each group was estimated as 37 for duration, 22 for stool rate and 25 for viral excretion to detect a difference of this magnitude at 5% significance and 80% power. The highest sample size of 37 for each group was adopted and with an allowance for a ~10% dropout rate, the total sample size was calculated to be 80.

Statistical analysis. The quantitative outcome measures (stool output, ORS intakes, frequency of stool) were compared by Student's *t* test. The Mann-Whitney *U* test was used to compare data not normally distributed. Dichotomous outcome measures were compared by chi square test. Duration of clearance of the pathogen was evaluated using life table survival curve.

RESULTS

Of the 240 children initially screened, 85 children (35%) whose stools were positive for rotavirus by ELISA were enrolled and randomized to receive therapy. Two children (1 in each group) whose stool was positive for rotavirus as well as *V. cholerae* was excluded as were 2 children (1 in each group) with severe oral candidiasis and 1 child (IIBC group) whose parents withdrew their consent during the study period. The data for the remaining 80 children (40 IIBC, 40 placebo) were analyzed. Admission characteristics relating to anthropometry, nutritional status, diarrheal duration with frequency of stool and laboratory values were comparable for the two groups of children (Table 1).

The children receiving IIBC consumed significantly less ORS on Days 2 ($P = 0.02$) and 3 ($P = 0.03$) of intervention. The total intake of ORS during the 4 days

was also significantly less in the IIBC-treated groups ($P = 0.01$). A significant reduction in total duration of diarrhea in children treated with IIBC compared with those with placebo was also observed. The daily and cumulative 4-day stool frequency was also significantly less in the IIBC-treated children than in their placebo counterparts (Table 2).

Stool output (grams/kg/day) was significantly less in IIBC-treated children than in controls on Day 1 ($P = 0.006$), Day 2 (0.006) and Day 3 (0.02) of the study period. However, the mean stool output on Day 4, when most of the children had recovered, was equivalent between the two groups. The children receiving IIBC also showed significantly less cumulative stool output, 31% lower during the 4 days, than did the controls ($P = 0.01$) (Fig. 1). The number of children whose illness resolved within 4 days of therapy was also greater in the IIBC-treated than in the placebo group (33 vs. 21; $P = 0.001$) (Fig. 2). Life table survival analysis showed that the probability of persistence of rotavirus in stools was significantly less in children treated with IIBC than in those treated with the placebo ($P = 0.001$) (Fig. 3). Fifty percent of the control children continued to have rotavirus in their stool on Day 4, whereas 95% children in the IIBC group no longer had detectable virus.

DISCUSSION

This study was conducted in children with moderate to severe rotavirus diarrhea to evaluate the clinical efficacy of orally administered immunoglobulin from IBC. Therapeutic use of antirotavirus immunoglobulin has been limited because of the paucity of data from a well-controlled study. The results of our study clearly demonstrated that treatment with the IIBC preparation significantly reduced diarrheal stool output compared with the placebo treatment during the study period. Reduction of stool volume was accompanied by significant reduction of frequency of the stool and requirements for ORS in the IIBC-treated children. No potential adverse effects of the IIBC were apparent in the study children. Because the number of breast-fed children was equal in both groups (exclusively breast-fed, 2 vs. 1; breast fed plus complementary fed, 36 vs. 38) (Table 1), the clinical improvement noted in the IIBC group was likely due to the IIBC.

Although the results are consistent with an earlier observation by Mitra et al.,¹⁵ there were certain important differences in the immunoglobulin preparation and its administration in the two studies. First Mitra et al. used a crude colostrum containing immunoglobulin along with lactoferrin, lactoperoxidase and oligosaccharides and required 300 ml/day (equivalent to 10 g of immunoglobulin) to accord clinical benefit. In contrast we used a bovine colostrum concentrate containing immunoglobulin dry powder which was more

TABLE 1. Baseline characteristics of the study children*

Variables	IIBC (n = 40)	Placebo (n = 40)
Age (mo.)	10.1 ± 4.7†	9.8 ± 3.3
Weight (kg)	7.5 ± 1.2	7.3 ± 0.8
MUAC (cm)	13.4 ± 1.1	13.3 ± 1.1
TSF (mm)	7.0 ± 1.2	6.8 ± 1.1
W/H	89.5 ± 8.8	87.5 ± 8.0
W/A	81.1 ± 11.3	79.1 ± 8.1
Duration of diarrhea (h)	29.0 ± 8.4	29.3 ± 9.6
Stool frequency last 24 h (n)	15.0 ± 6.0	17.2 ± 9.0
Family income (US\$)/mo.	80.1 ± 10.2	76.3 ± 12.5
Feeding habit		
Exclusively breast-fed	2	1
Breast-fed + complementary-fed	36	38
Solid food	2	1
Serum electrolyte (mmol/l)		
Sodium	135.6 ± 3.1	136.3 ± 3.9
Potassium	4.2 ± 0.7	4.4 ± 0.8
Chloride	110.5 ± 3.1	109.1 ± 2.7
Total carbon dioxide	14.9 ± 3.0	14.7 ± 3.4
Temperature (°C)	37.4 ± 0.32	37.6 ± 0.76
Total WBC/mm ³	12 120 ± 3436	13 070 ± 5804
Stool rates (ml/kg/4 h) during observation period	36 ± 19	40 ± 20

* Values are not significant between groups.

† Mean ± SD.

MUAC, mid-upper arm circumference; TSF, triceps skinfolds thickness; W/H, weight for height; W/A, weight for age; WBC, white blood cells.

TABLE 2. Daily intakes of ORS, stool frequency and duration of diarrhea in children treated with IIBC or placebo

Variables	IIBC (n = 40)	Placebo (n = 40)	P	95% CI for Difference
ORS intake (ml/kg/day)				
Day 1	87 ± 10*	105 ± 10	0.08	-39; 2
Day 2	78 ± 14	115 ± 14	0.01	-64; -9
Day 3	62 ± 10	110 ± 14	0.005	-81; -15
Day 4	54 ± 11	84 ± 12	0.06	-61; 1
Total (Days 1-4)	281 ± 30	410 ± 39	0.001	-227; -30
Duration (h) of diarrhea after HBC or Placebo	72.6 ± 38.9†	96.4 ± 46.7	0.016	-43; -5
Frequency of stool (no./day)‡				
Day 1	9 (6, 13)	12 (9, 18)	0.02	-6; -1
Day 2	7 (5, 12)	12 (7, 17)	0.001	-6; -1
Day 3	6 (3, 9)	10 (5, 14)	0.02	-6; 0
Day 4	4 (3, 4)	7 (3, 12)	0.03	-4; 0
Total (Days 1-4)	29 (18, 39)	42 (27, 58)	0.007	-20; -3

* Mean ± SEM.

‡ Mann-Whitney U test; values are median (quartile).

CI, confidence interval.

† Mean ± SD.

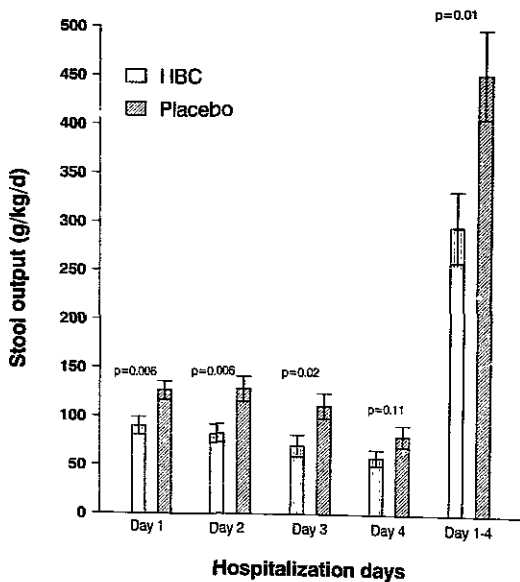


FIG. 1. Mean daily stool output (grams/kg/day) in children with immunoglobulin from IIBC or placebo. Bars, SE.

potent, was easily dispensable and required relatively lower doses (3.6 g of immunoglobulin) to achieve benefit. Second the product used in the study of Mitra et al. was initiated relatively late in the disease process, i.e. a mean period of 46 h after the onset of illness. Therefore the success of the HBC in the study by Mitra et al. could in part reflect the natural course of the disease and be attributed to the self-limiting process of the illness. In this study we had a better opportunity to test the effectiveness of the IIBC during the peak period of illness as the product was initiated after a mean of 29 h of onset.

Another noteworthy finding of the present study was an earlier and significant reduction in duration of apparent rotavirus excretion in the IIBC-treated group

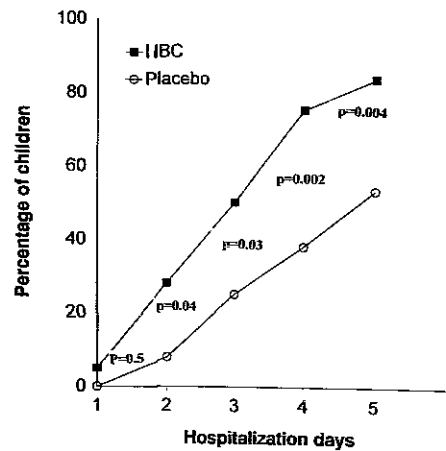


FIG. 2. Comparison of recovery from diarrhea in children treated with IIBC or placebo.

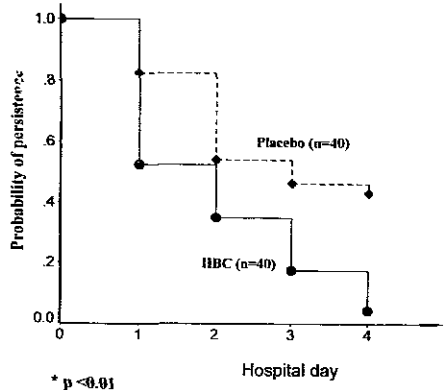


FIG. 3. Probability of clearance of rotavirus from stools in children treated with or without IIBC.

(Fig. 3). This finding, which is also in agreement with those of Hilpert et al.¹¹ and Ebna et al.,¹⁴ is important from a public health perspective with regard to rotavi-

rus transmission within communities and hospitals because of the high secondary attack rates in rotavirus gastroenteritis outbreaks.¹⁹ The findings of our study are also consistent with those of a double blind, placebo-controlled trial with orally administered human serum immunoglobulin to children with rotavirus diarrhea.²⁰

Brunser et al.,²¹ however, had observed no positive effect of supplementing infant formula with bovine milk immunoglobulin concentrate against rotavirus in a small scale field trial. The failure probably relates to the very low level of antibody (1%) in the formula.

The clinical benefits of IIBC might indicate that IIBC remained active while passing through the gastrointestinal tract and therefore support the observation by Zinkernagel et al.²² that IgG1 resists degradation during transit through the human intestine. Although we started treatment with IIBC within a relatively short period of onset of diarrhea, it is conceivable that the impact of IIBC could be enhanced if treatment is initiated even earlier.

The dosage of bovine oral immunoglobulins needed to obtain therapeutic efficacy is still to be determined. The 10-g daily dose of immunoglobulin in 300 ml of bovine colostrum for 3 days as used by Mitra et al.¹⁵ was similar to that of previous studies with HBC in *Cryptosporidium* infection in humans.²³ A daily dose of 500 mg of immunoglobulin was sufficient as prophylaxis against rotavirus diarrhea.²⁴ In our study we observed a therapeutic effect using 3.6 g/day for 4 days. Clinical benefit was also observed with equivalent amounts in earlier therapeutic trials against infection caused by *H. pylori*²³ and cryptosporidia,²⁵ suggesting that a 3.6-g daily dose is sufficient and could be recommended for clinical use. However, because the cost for this regimen is substantial, efforts to determine the lowest effective dose for immunoglobulins are warranted to optimize treatment.

The mechanisms of IIBC to reduce stool output and virus excretion, as observed in our study, are not fully understood. Competitive inhibition of the binding of luminal toxins by orally administered antitoxin antibodies might be a plausible mechanism of reduced stool output. Our preparation contained only a small concentration of antibodies against the viral enterotoxin,²⁶ nonstructural glycoprotein, NSP4, which promote and augment cyclic AMP-dependent Cl⁻ secretion and diarrhea.²⁷ The major clinical effect of the product used in our study was probably not a result of neutralization of the toxin but instead of an influence on the virus particle itself.

The mechanism of antirotavirus efficacy of serum immunoglobulin given orally has been investigated in a recent *in vitro* study with Gaco-2 cells infected with rotavirus. In this model immunoglobulin addition to

infected cells partially prevented the decrease in trans-epithelial electrical resistance and induced a later shift of transepithelial electrical resistance toward increasing values, suggesting restoration of the integrity of the monolayer.²⁸ The antiviral activity of the preparation was dose-dependent, and its efficacy was found to be related to its early administration. It is possible that by neutralizing activity against the virus, IIBC prevented or counteracted the modifications in epithelial cells induced by rotavirus and thereby enhanced recovery.

In conclusion antirotavirus antibody from colostrum of immunized cows was effective in the treatment of rotavirus gastroenteritis in children. IIBC reduced stool output and resulted in early recovery from illness and early clearance of viruses from stool. No adverse effects were observed from the oral administration of the products in this study. These results suggest that clinical application of IIBC might soon provide a therapeutic option for rotavirus diarrhea afflicting millions of children worldwide.

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Enterococcal bacteremia in children: a review of seventy-five episodes in a pediatric hospital

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Background. Enterococcal bacteremia is being increasingly reported. Although there have been a number of recent studies of enterococcal bacteremia in adults, there are few studies involving children. We carried out a prospective study to determine the epidemiologic, clinical and laboratory characteristics of such bacteremia in children.

Methods. Clinical and microbiologic data were

recorded prospectively for all episodes of enterococcal bacteremia occurring during a 3-year period between January 1, 1995, and December 31, 1997.

Results. Seventy-five episodes of enterococcal bacteremia occurring in children at our institution during a 3-year period were prospectively analyzed. Serious underlying disease was present in 67 (89.3%) episodes, and in 48 (64%) episodes patients had received antibiotics during the 2 weeks preceding enterococcal bacteremia. Forty-seven (62.7%) episodes were nosocomial in origin and 26 (34.7%) were polymicrobial. Fifty (66.7%) episodes occurred in children 1 year old or less. A source of bacteremia was identified

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