

B 221, a medical food containing antisecretory factor reduces child diarrhoea: a placebo controlled trial

Shakila Zaman (zaman.shakila@gmail.com)¹, Javaria Mannan², Stefan Lange³, Ivar Lönnroth³, Lars-Åke Hanson⁴

1. Health Services Academy, Islamabad, Pakistan

2. Departments of Social and Preventive Paediatrics, Fatima Jinnah Medical College, Lahore, Pakistan

3. Department of Clinical Bacteriology, University of Göteborg, Göteborg, Sweden

4. Department of Clinical Immunology, University of Göteborg, Göteborg, Sweden

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Correspondence

Shakila Zaman MD PhD, Director, Health Services Academy, Islamabad, Pakistan.

Tel.: +92-51-9255590-4

Email: zaman.shakila@gmail.com

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Abstract

Aim: We investigated whether egg yolk in the form of B221 (Salovum), a medical food containing antisecretory factor (AF) might be used for treatment of acute and prolonged diarrhoea.

Methods: 240 children 6–24 months of age, half with acute diarrhoea (<7 days) and half with prolonged diarrhoea (≥7 days) were randomly given 2 g of B221 or placebo every 5 h for 3 days, added to an oral rehydration salt solution.

Results: B221 reduced the number of stools in the acute diarrhoea group compared with placebo (day 3, $p = 0.0054$). Stools normalizing in consistency (day 3, $p = 0.053$) and recovery within 3 days was commoner in the B221 group ($p < 0.001$). A successful outcome was recorded in 82.8% in the B221 group, compared to 54.4% in the placebo group. In the group with prolonged diarrhoea the stool consistency normalized earlier in the patients receiving B221 than in the patients receiving placebo ($p = 0.008$). A successful outcome was obtained in 90.9% and 63.2%, ($p = 0.0011$) in the B221 and placebo-treated groups respectively.

Conclusion: B221, which is a medical food, can be used to significantly improve the condition of children with acute, as well as prolonged diarrhoea caused by a broad range of undefined pathogens.

INTRODUCTION

Diarrhoeal diseases still remain a predominant problem in children living in less privileged populations (1). Although most of the illness consists of acute diarrhoeal episodes, 5% of them may prolong into a more chronic form of intractable diarrhoea (2). Severe malnutrition and ensuing infections are mainly responsible for the premature and preventable deaths in these young children. The prolonged episodes of diarrhoeal illness causes much more damage than the acute ones (3). For instance, 20% of the deaths in children under 5 years of age were shown to be associated with diarrhoea and then in 2 out of 3 cases with prolonged/chronic diarrhoea (4). In a cohort from Lahore of 1496 newborns during a follow-up till 5 years, we showed that at least 14–17% of the acute diarrhoeal episodes resulted in prolonged diarrhoea and 80% of the infant deaths had underlying malnutrition (5).

In view of the above, with concentrated efforts to promote optimal breastfeeding practices of the mothers living in the city slums, we could reduce the number of diarrhoeal episodes, but the severity and prolongation in the several cases still occurring requires more intensive measures (6).

Antisecretory factor (AF) is a protein present in most tissues in the body (7),(8). The plasma level of AF can be increased by exposure to bacterial enterotoxins (9) and to specially processed cereals (10). These cereals when fed to lactating mothers, have given increased milk levels of AF and protection against mastitis (11). The antisecretory effect

of AF has been shown in patients with secretory diarrhoea of endocrine origin (12) and an antiinflammatory effect of AF has also been demonstrated in ulcerative colitis (13) and Crohn's disease (14).

The aim of the present placebo controlled randomized clinical trial was to test the efficacy of feeding egg yolk powder B221, containing AF-rich egg yolk, from hens that were fed the specially processed cereals (15),(16), to children from 6–24 months of age presenting with acute, or prolonged diarrhoeal episode. Efficacy was measured in terms of severity of diarrhoeal illness, i.e. frequency of diarrhoeal stools and their consistency while duration was measured as the number of days taken to normalize stooling during a 3 days stay in the hospital. The response to B221 can provide opportunities for immediate and effective measures to reduce the severity and the duration of the disease in young children.

METHODS

Trial design

The trial was carried out at the Department of Paediatrics at Sir Ganga Ram Hospital, Fatima Jinnah Medical College, Lahore, Pakistan. The study duration was 12 months (September 2004–September 2005) including two diarrhoeal seasons. The patients had to fulfil the following criteria to become eligible for recruitment before randomization: The age of the patients had to be between 6–24 months so that exclusive breastfeeding was not influenced in this baby-friendly hospital. The diarrhoeal illness

should not have exceeded 7 days at the time of recruitment to the acute diarrhoea group. If the diarrhoeal episode was reported to be more than 7 days then the children were recruited into the prolonged diarrhoeal group. Any child requiring life-saving measures was not included in the study. Special care was taken to exclude any known allergies to eggs and other food items.

The diarrhoeal patients were identified from the Outpatient Clinic and from the Emergency Ward of the Paediatrics Department. Sampling frames were drawn by listing the patients, n = 120 for the acute and n = 120 for the prolonged diarrhoea group. Within each of these two groups, a list was drawn for 60 patients using the random number tables allocating them to the active group (AF Group, B221) and the rest were allocated to the placebo group (non-AF Group, placebo). The inclusion of the patients was ensured so that no patients fulfilling the inclusion criteria were missed. Compliance to the intake of the drug or placebo was controlled by admitting them in the wards and by supervising the intake by trained Paediatric nurses/Lady Health Visitors (LHV).

Sample size

To be able to improve the diarrhoeal illness in terms of reducing the frequency of diarrhoea by at least 20%, with a probability of achieving this result with 95% confidence interval and an alpha level of 5%, a sample size of 52 patients in each group was calculated. Keeping a margin for refusals and dropouts, 60 patients in each group for acute and prolonged diarrhoea were recruited initially reaching a sample size of 240.

The study population

1. The group with acute diarrhoea is shown in Table 1. The initial recruitment was aimed at 60 cases into each of the treatment or placebo subgroups. Four patients were at first incorrectly recruited into the prolonged diarrhoea group, but based on the number of days with diarrhoea they were included in the acute diarrhoea group. There

Table 1 The trial profile of patients with acute diarrhoeal episodes

	B221 group	Placebo group
Initial recruitment	60 1 refused	60 3 refused
Day 1	64* 4 left against medical advice 1 refused	57 3 left against medical advice
Day 2	59 21 discharged**	54 17 discharged 2 left against medical advice
Day 3	38	35

*Four children were initially recruited in a study of prolonged diarrhoea, but when reviewed, were found to have acute diarrhoea, so they were included in this group of study.

**As soon as the children showed signs of clinical improvement: reduced purging and improved hydration, they were discharged.

Table 2 The trial profile of children with prolonged diarrhoeal episodes

	B221 group	Placebo group
Initial recruitment	60 5 refused	60 3 refused
Day 1	55 1 discharged**	57 4 left against medical advice
Day 2	54 16 discharged	53 8 discharged 1 left against medical advice
Day 3	38	44

**As soon as the children showed signs of clinical improvement: reduced purging and improved hydration, they were discharged.

was one refusal on day 1 in the B221 group, whereas the placebo group had three initial refusals and five leaving against medical advice on days 1 and 2. Twenty-one patients were discharged on day 2 in the B221 group as recovered, compared to 17 recovered discharges taking place in the placebo group simultaneously. By the end of 3 days stay in the hospital, there were 38 and 35 patients in the two groups respectively.

2. The group with prolonged diarrhoea is shown in Table 2. The initial recruitment was aimed at 60 patients in each subgroup for treatment or placebo. Five and 3 mothers, respectively in the 2 groups, refused participation so that 55 and 57 patients were left to start with. On day 1, 1 patient was discharged in the B221 group as recovered, while 4 patients left the hospital against medical advice in the placebo group. On day 2, 16 patients were discharged from the B221 group as recovered, while 8 recovered patients were discharged from the placebo group, and 1 left against medical advice in this group. On day 3, 38 and 44 patients were left in the two groups.

The mothers of the children included in the study were informed about the study and a written consent was taken.

The children were listed as they came for consultation. They were allocated to either the B221 group or the placebo group according to the numbers in the list randomizing them into two groups, the B221 group receiving sachet 'A' and the other group, the placebo group receiving sachet 'B'. Sachet A contained B221 sprayed dried egg yolk from hens fed AF-inducing specially produced cereals as previously described (15) and sachet B contained sprayed dried egg yolk powder from hens not fed with AF-inducing food. The placebo product was tested not to contain AF (13).

Both the sachets looked exactly the same except for the A and B written on them for ease of administration by the trained team of LHVs who were blinded to the contents of the sachets. The paper with the information on sachets was kept only by the PI.

A complete history and examination of the recruited children before the therapy was recorded on the predesigned proforma. The days of diarrhoea, the frequency and consistency of stoolings, thirst and urinary output were recorded.

The frequency of passage of urine at least 6 times during the last 24 h was graded as adequate. The status of the fontanelle, mucous membranes and skin turgor was also noted as was weight, length, respiratory and heart rates.

The recruited children, with acute and prolonged diarrhoea, were fed 2 g of egg yolk every 5 h under the supervision of the LHV as soon as they were admitted to the ward and consent obtained. The powder was mixed in 20 mL of rehydration solution and fed to the child orally every 5 h. All the parameters were noted during the stay and recorded at the end of 5 h. The time of administration was for the first 3 days.

The intervention was stopped at the end of 3 days irrespective of the kind of response shown by the patients. All the children continued with the standard protocol of management of diarrhoeal illness as practiced in the ward.

The patients were discharged as recovered on the basis of the following clinical criteria: the frequency of stooling reduced to less than 5 stools/day and the consistency of the stools becoming normal and the child being able to continue to take the rehydration solutions and food at home. During the hospital stay whenever the criteria were met, patients were discharged.

After the written consent, the children were followed in the ward by the trained LHVs throughout 24 h. The feeding of egg yolk was carried out by the LHVs with 1 doctor supervising them. The nature of therapy was not disclosed to the LHVs, the doctor, or the mothers. The mothers knew that they were part of a study where egg yolk was to be fed to the sick children, hence compliance was not a problem. They examined and recorded the stools for consistency and frequency during the 3 days round the clock. The training of the LHVs was undertaken before and during the period of study.

The permission to conduct the study was obtained from the Ethics' committee at Fatima Jinnah Medical College, Lahore, Pakistan.

Statistical analysis

The variables studied are presented as proportion (%) and mean with standard deviations between the two groups. Two means were compared using a *t*-test and the two proportions were tested using a Chi-square test. The level of significance was chosen at a probability of 0.05 in two-tails. ANOVA was also run on the variables with and without various categories to confirm the findings. Weight and length were converted into standard deviation scores (SDS) using WHO/NCHS standards adjusting for gender and age.

The analysis was carried out after the data were collected without knowing which sachet contained the AF in the two categories of acute and prolonged diarrhoea. This code was only known after the analysis was completed.

RESULTS

Acute diarrhoea

The comparability of the two, B221 and placebo, groups as to the demographic details on initial presentation regarding

the disease and clinical examination is detailed in Table S1a. Mean age in the two groups did not show any difference ($p = 0.81$). The distribution of gender was also the same in the two groups, showing a predominance of male children in both groups. The days from onset of diarrhoea before admittance as to frequency of stools, consistency of stools, thirst, urinary output, heart rate and respiratory rate did not show any statistically significant differences. The mean nutritional status (weight/length SDS) was similar in the two groups.

Table S2a shows the mean frequency of stools of 11.5 ± 6.6 in the B221 group compared to 15.7 ± 8.2 in the placebo group on day 1 ($p = 0.0024$). On day 2, the mean frequency of stools was 7.3 ± 5.0 compared to 10.5 ± 7.4 in the placebo group ($p = 0.007$), while on day 3 the mean frequency was 4.8 ± 4.1 stools/day compared to 8.0 ± 5.5 stools/day in the two groups respectively ($p = 0.0054$). Similarly, the consistency of stools on day 1 in the B221 group was 34.4% with watery stools compared to the placebo group with 68.4% having loose consistency ($p < 0.001$). On day 2, this difference was 13.6% compared to 38.9% in the two groups ($p = 0.013$). On day 3, 57.9% had normal consistency in the B221 group compared to 28.6% in the placebo group ($p = 0.053$). The mean number of days with diarrhoea in the two groups were 2.6 ± 0.6 and 2.8 ± 0.7 showing a statistically non-significant difference ($p = 0.155$). Thirst did not show any consistent change with therapy. The urinary output was the first symptom of repair in the two groups.

Table 3a shows the early changes in the consistency and frequency of stools in 24 h that took place in the individual patients and were categorized into successful therapy, failed therapy, or if the patients left against medical advice, labeled as inconclusive. Those parents who refused to continue the study were not satisfied with the general response of the therapy. The therapy was successful in 53/64 (82.8%) in the B221 group compared to 31/57 (54.4%) in the placebo group ($p < 0.001$). The failures were also significantly more common in the latter group (36.8%) as compared to the B221 group (10.9%), ($p < 0.001$).

Prolonged diarrhoea

The comparability of the two groups as to demographic details on initial presentation regarding the disease and clinical examination is detailed in Table S1b. Mean age in the two groups was 15.2 ± 6.1 and 12.8 ± 5.5 months showing a

Table 3a The outcome of the trial at the end of 3 days was evaluated based on the response of the individuals with acute diarrhoea to the active compound/placebo, respectively. Successful outcome corresponds to the consistency of stools being back to normal and the number of stools being reduced to ≤ 5 /day

Outcome	B221 group	Placebo group	p-value
Successful	53 (82.8)	31 (54.4)	<0.001
Failure	7 (10.9)	21 (36.8)	<0.001
Inconclusive*	4 (6.3)	5 (8.8)	0.733

*Nine children from the two groups left against medical advice, hence their outcome was considered as inconclusive.

Table 3b The outcome of the trial at the end of 3 days in the patients with prolonged diarrhoea evaluated as in Table 5a.*

Outcome	B221 group	Placebo group	p-value
Successful	50 (90.9)	36 (63.2)	<0.001
Failure	5 (9.1)	16 (28.1)	0.010
Inconclusive*	0	5 (8.8)	0.019

*Five children left the hospital against medical advice, hence their outcome was considered as inconclusive.

significant difference ($p = 0.04$). The distribution of gender showed a higher proportion of males, but the differences were not significant. The days from onset of diarrhoea before admittance, frequency of stools, consistency of stools, thirst, urinary output, heart rate and respiratory rate did not show any significant differences between the groups. The mean nutritional status (weight/length SDS) was similar in the two groups.

Table S2b shows that the mean frequency of stools on day 1 was 11.9 ± 7.0 in the B221 group compared to 12.9 ± 8.2 in the placebo group ($p = 0.48$). On day 2, the mean frequency of stools was 8.5 ± 5.8 in the B221 group compared to 8.7 ± 7.4 in the placebo group ($p = 0.76$), while on day 3 the mean frequency of stools was 5.3 ± 4 stools/day compared to 6.0 ± 4 stools/day in the placebo group ($p = 0.31$). The consistency of stools at day 1 in the B221 group was 36.4% with watery stools compared to 42.1% in the placebo group ($p = 0.66$). At day 2, this difference was not statistically different in the two groups ($p = 0.85$), while on day 3, none of the children in the B221 group had watery stools, compared to 9.1% still passing watery stools in the placebo group ($p = 0.14$). The mean number of days with diarrhoea in the two groups were 2.7 ± 0.5 and 2.9 ± 0.4 showing a statistically nonsignificant difference ($p = 0.14$). Thirst and urinary output did not differ between the two groups over the 3 days.

Table 3b shows a statistically significant difference ($p = 0.0011$) in the success of the therapy in the B221 group (90.9%) as compared to the placebo group (63.2%). There were 9.1% failures in the B221 group compared to 28.1% in the placebo group ($p = 0.01$). However, there were 8.8% cases in the latter group where the outcome was inconclusive since these mothers had left against medical advice.

DISCUSSION

This randomized, placebo controlled trial shows that feeding a medical food, B221, containing AF, to young children with acute diarrhoea resulted in significant improvement in the frequency and consistency of diarrhoea. Although a change could also be seen in the number of days with diarrhoea, the difference was not significant possibly since the study was limited to 3 days of therapy. For the patients with prolonged diarrhoea, the change in the consistency of the stools to normal was seen more frequently among the group treated with B221. A clinically successful outcome was seen in 91% of the patients in the B221 group compared to 63% successful outcome in the placebo group.

The recruitment criteria were strictly followed by the trained staff in the hospital. The follow-up was close and the compliance in feeding the egg yolk powder, whether active or placebo, was maximized by trained LHVs who were present 24 h/day with the patients. The management therapy was the same for all the patients and the ward protocol was followed for all the cases in a similar fashion. All these patients could have been treated at the outpatient level, but were brought to the inpatient ward to be able to correctly record the variables and for reliable compliance of the therapy. The LHVs did not know what was in the sachets A and B. They could identify the early response in patients receiving sachet A, but since some of the patients in group B also showed a good response to the rehydration treatment given in both groups, the identity of the active compound was not revealed. The number of patients recruited was also at a pace which kept them busy, which may have added to keeping them blinded to the drug during the study period.

The nutritional status of the recruited children was the same in the two groups on admittance and the change over the 3 days, although measured, was not substantial enough to show a significant difference. Hence, that aspect is not shown in the results. The intake of fluids and foods during the stay in the hospital was recorded carefully, but no significant differences were seen in the two groups. Most mothers were hesitant to start feeding their children the foods, which were promoted as part of the nutritional counselling the LHVs were carrying out for the mothers in the ward. The mothers waited till they were back at home to start with the recipes taught to them in the hospital.

The importance of feeding B221 to the patients with acute and prolonged diarrhoea can be considered as a prospect of the future. We started by giving small doses of B221 every 5 h not yet knowing the optimal dose. This study was an attempt to try a small dose via a route which was acceptable to the mothers and the hospital staff. It has shown a considerable effect. Different doses need to be tested and other routes made available in a hospital situation, e.g. nasogastric feeding especially for children with prolonged diarrhoea, who have added mucosal damage and malnutrition.

It is highly unlikely that all patients participating in the present study were infected by the same diarrhoeic agent. Conclusively, AF inhibits diarrhoeal diseases of various etiologies, and the AF mechanism of action must be inhibitory to a wide variety of diarrhoeic disturbances. Part of the explanation behind this broad biological reactivity might be the net result of AF binding to flotillin-1 (17), a component making up lipid rafts in the cellular membrane. Lipid rafts are cholesterol rich specialized areas in the plasma membrane with a high content of receptors, ion channels and various forms of other biological transport channels. Thus, binding of AF to flotillin-1 might be followed by a changed transport activity of the lipid rafts components (18), i.e. aquaporins (19). Aquaporins are important regulators of water transport in the gastrointestinal tract (20) and by regulating the activity of these structures AF could exert its antisecretory activity, independently of the pathogens causing the disease. This hypothesis is clinically supported by the present results.

Our study gives good support to that B221 has useful effects in diarrhoeal illness in infants and young children. Higher doses of B221 may provide even more convincing evidence for the usefulness of AF in the management of the acute diarrhoeal episode where 17–19% of the episodes may result in prolonged diarrhoea, especially in a childhood population with a high malnutrition rate (2). Thus, effects of B221 against both acute and prolonged diarrhoea might come to great use in many populations with a high risk of morbidity and mortality in these diseases.

The AF-containing egg yolk powder B221 is a medical food and not a drug, simplifying its use and availability. In addition, its use might be followed up with intake of specially processed cereals (SPC-Flakes®) which effectively induces endogenous production of AF in the child (21). These cereals can also be used for prophylaxis in much exposed populations, especially during the diarrhoea season.

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Supplementary material

The following supplementary material is available for this article:

Table S1a The demographic and clinical characteristics of the patients with acute diarrhoea.

Table S1b Showing the demographic and clinical characteristics of the patients with prolonged diarrhoea.

Table S2a The changes occurring during the course of 3 days of hospitalization in patients with acute diarrhoea.

Table S2b The changes occurring during the course of 3 days of hospitalization in patients with prolonged diarrhoea.

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