Effect of Micronutrients on Morbidity and Duration of Hospital Stay in Childhood Pneumonia

*Wahed MA[1], Islam MA[2], Khondakar P[3], Haque MA[4]

A cross-sectional and controlled clinical trial was conducted in under-5 children to compare the effects of supplementation of five micronutrients (vitamin-A, vitamin C, vitamin E, folic acid and zinc) on the morbidity and on the duration of hospital stay in pneumonia. Data were collected from 1150 children. Among them 350 children were excluded for various reasons and finally data from 800 children were analyzed. Among these 800 children 59.00% (475) were male and 41.00% (325) were female. The mean±SD age was 6.5±5.6 months and 56.25% (450) were infants. The children were divided into two groups-400 in control group and 400 in intervention (case) group. In both the groups, specific treatment was given by ampicillin and gentamycin. In intervention group, five micronutrients were given in 200 children from the day of admission and continued up to discharge. Another 200 children were again divided into 5 sub-groups (40 in each sub-group) and a single micronutrient was given in the same way in each sub-groups. All the subjects were suffering clinically from severe pneumonia and radiologically from bronchopneumonia. Cases and controls were matched by parents' occupation, education level, economic status and family members. All the children were fully vaccinated as per existing EPI schedule of the country, partially breastfed up to six months and after six months weaned by carbohydrate rich diet. All the children were in mild (grade I) PEM according to Gomez's classification. Venous blood was collected for estimation of serum level of five micronutrients from all the samples before starting treatment by standard procedures. The average blood level of all the micronutrients was low. The average duration of hospital staying was 6.75 days in intervention group and 7.75 days in control group ($p<0.01$). Chest indrawing and fast breathing disappeared earlier in the intervention group ($p<0.01$) suggesting that supplementation of micronutrients decrease the morbidity and duration of hospital stay of children suffering from pneumonia.

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Key words: Pneumonia, Micronutrient supplementation, Morbidity

Introduction

Acute Respiratory Infection (ARI) is the most common cause of morbidity of under-five children in Bangladesh and a great public health concern[1,2]. Among all the ARI's, pneumonia occupies special attention because of a significant proportion of childhood mortality occurring due to this ailment[3,4]. On average, children have 4-6 ARI episodes each year; 5-8 episodes per child per year in urban areas and 3-5 in rural areas[4-6]. One third of all admissions in hospitals of children are sufferers from ARI and there are 85,000 deaths due to pneumonia each year in Bangladesh[7-9].

On the other hand, many children suffer from deficiency of micronutrients and more than 2 billion children are sick or disabled as a result of micronutrient deficiency in the world and a major portion are in the South-East Asia including Bangladesh[10]. Vitamin A deficiency causes epithelial defects, impairs the immune system and reduces children's resistance to diarrhoea, measles and increases the incidence and severity of pneumonia[11,12].

1. *Dr MA Wahed, Associate Professor, Department of Paediatrics, Rangpur Medical College, Rangpur, Bangladesh; E-mail: mawahed@mail.mayaonline.net.bd
2. Professor Md Anwar Ul Islam, Professor of Pharmacy, University of Rajshahi, Rajshahi, Bangladesh
3. Mrs Proma Khondakar, Associate Professor, Department of Pharmacy, University of Rajshahi, Rajshahi, Bangladesh
4. Dr Md Azizul Haque, Associate Professor, Department of Paediatrics, Mymensingh Medical College, Mymensingh

*for correspondence

Zinc acts as an immunomodulant and its deficiency is associated with increased prevalence and delayed recovery from pneumonia. In a trial in our country on children aged 6-12 months of age, simultaneous weekly administration of zinc and iron was associated with 40% lower risk of severe pneumonia[13,14]. Supplementation of zinc has also been found to reduce risk of pneumonia by 45% and duration of hospital staying by 41%[15-17]. Folic acid, Vitamin C and Vitamin E play roles as antioxidant and decrease the severity of pneumonia by protecting the damage of cells and tissues from oxidants. A study conducted on infants and young children with vitamin C at a dose of 500mg IM six to twelve hours interval showed that 3-7 injections gave complete clinical and x-ray response in case of virus pneumonia[18].

So, it is obvious that there is relationship between incidence and severity of pneumonia and micronutrient deficiency. Moreover, micronutrient deficient children require more admission in the hospital and more costly drugs are needed and they also require longer time in hospital[5,7,8]. This causes loss of resources from the parents because Government Hospitals usually run short of costly drugs and maximum numbers of these drugs are usually bought by the parents from outside shops[19]. In Bangladesh, only few studies were conducted to assess the micronutrient supplementation on morbidity of pneumonia in under-five children. For this reason, the study was conducted to compare the effects of supplementation of micronutrients on the severity of pneumonia and duration of hospital stay.

Methods

The study was a cross-sectional, prospective and controlled micronutrient supplementation trial. The study was conducted in the Paediatrics Department of Rangpur Medical College Hospital for a period of three years from 1st July 2004 to 30th June 2007. All the children admitted with various types of pneumonia were the study population and among these, children having the clinical diagnosis of severe pneumonia and radiological diagnosis of bronchopneumonia on admission were selected as samples. The statistical formula $4\sigma^2/L^2$ was applied to determine the number of samples. Here σ was the standard deviation of average stay in hospital, ±4.8 in this study and L was acceptable variation, 0.5 day in this study at 95 % confidence interval[20,21,22]. In this way, the optimum number of samples became 384. This was rounded to 400 and then doubled (400×2 = 800) since there were two independent groups. The sampling method was systematic sampling and every 1st patient was given the intervention and 2nd patient was treated as control from a prepared register.

A standard questionnaire was developed in accordance with the study objectives to obtain relevant information. The questionnaire contained some independent variables such as age, educational status of the parents, monthly family income of the parents, breast feeding pattern, time and type of weaning foods, immunization status, vitamin A supplementation, vitamin C supplementation, vitamin E supplementation, supplementation of folic acid, supplementation of zinc and weight of the child. The dependent (outcome) variables were morbidity from pneumonia and duration of hospital stay in days. Few months before starting the formal study, the questionnaire was pre-tested among children of the ward. During pre-testing, all the variables were considered except collection of the blood. Then it was modified as required and finalized for collection of data. The Questionnaire was in English language.

History of illness of the child was collected from the mother or guardian who attended the child in hospital. Clinical examination was carried out on the child on the day of admission and everyday up to discharge. The 'Bar Scale' designed by National Nutritional Council of Bangladesh was used to record the body weight. All the questionnaires were filled by the investigator himself. The children who left the hospital on 'risk bond' or 'absconded' form the ward or 'expired' during treatment were excluded from the analysis. Also those who developed a complication of pneumonia, were suffering from other severe systemic diseases with pneumonia, required antibiotics other than the ampicillin and gentamycin and whose parents did not give consent for drawing blood were also excluded from the study. The children who were in a convalescent stage from another disease and were taking or took any of the micronutrients within last one week also excluded. Initially data were collected from 1150 children and after exclusion only 800 children were selected for analysis.

Answers of the mothers and findings of clinical examinations were recorded in the "Interview Schedule". The nutritional status was assessed according to Gomez' classification. In all children, venous blood was taken before starting treatment. Then the blood was sent to the laboratory for centrifugation and separation of serum for estimation of serum level of micronutrients. The method of analysis was High Performance Liquid Chromatography (HPLC)[23-28] for vitamin A, vitamin C, Vitamin E, colorimetric method for zinc[29,30] and ELISA[31] for folic acid. The selected laboratories were Padma Diagnostic Center, Dhaka and Apollo Diagnostic Center, Rangpur. Tests were performed by the consultants experienced in the respective fields.

The children were followed daily up to discharge from the hospital. The criteria of discharge were free from the clinical features of severe pneumonia for two consecutive days. There were six groups of children- one was intervention group (N=400) and the other control group (N=400). Again the intervention group was broken into six groups (200 + 40 + 40 + 40 + 40 + 40). In intervention group, specific treatment was given by Ampicillin (50-100 mg/kg/day) and Gentamycin (5-7mg/kg/day) in injection for six days along with micronutrients in adequate doses. The brands of micronutrients were products of reputed Pharmaceutical companies. In 200 children, all the 5 micronutrients were given along with specific treatment but only one micronutrient was prescribed in each of 5 sub-groups (40 in each sub-group). In control group, only specific treatment was given without micronutrients. Compliance was checked by Assistant Registrar every day during ward rounds. The drugs were administered by mothers and nurses. Verbal or written consent was taken from the parents maintaining the principles of Helsinki Declaration[32,33].

After completion of collection of data, all filled up 'Interview Schedules' were checked for missing values and outliers. The data were then entered into a computer. The analysis was performed by SPSS+PC programme according to objectives. Descriptive statistical tests were applied to age, monthly income and biochemical variables. Univariate, multivariate and ANOVA were also performed as necessary.

Results

Among 800 children studied 56.25%(450) were infants, 23.75%(190) were within 1-2 years, 11.25%(90) were within 2-3 years age group, 6.25% (50) were 3-4 years age group and 2.50% (20) were 4-5 years age group. Infants suffered more from pneumonias. Of the study population 59.00% (475) was male and 41.00% (325) was female. The mean± SD age was 6.5±5.6 months (Table I). The average serum level of different micronutrients were vitamin A (retinol) 0.60 μmol/l, vitamin C (ascorbic acid) 32.50 μmol/l, vitamin E 6.50 μmol/l, folic acid 3.50 nmol/l and zinc 9.70 μmol/l. The average serum level of all the micronutrients considered was lower than the normal level (Table II).

Table I: Distribution of children according to age and sex (N=800)

Age group	Sex of the children		Total (%)
	Male (%)	Female (%)	
Birth-1 year	255 (31.88)	195 (24.37)	450 (56.25)
1-3 year	170 (21.24)	110 (13.74)	180 (35.00)
3-5 year	50 (6.25)	20 (2.51)	70 (8.75)
Total	475 (59.00)	325 (41.00)	800 (100.00)

Mean age± SD = 6.5 ± 5.6 months

Table II: Average baseline serum concentrations of micronutrients in the samples (n=800)

Item	Average (serum) level ± SD	Normal value
Vitamin A	0.60 ± 0.05μmol/l	00.70-1.50μmol/l
Vitamin C	32.50 ±0.15μmol/l	34.00-113.00 μmol/l
Vitamin E	6.50 ± 0.45μmol/l	7.00-21.00 μmol/l
Folic acid	3.50± 0.04nmol/l	4.10-20.40 nmol/l
Zinc	9.70 ± 0.74μmol /l	09.8-18.1μmol /l

ANOVA p<0.10 (Poorly significant)

The average duration of hospital stay of children in control group was 7.75 days and in intervention group was 6.75 days. The average difference was 12.90% (p<0.01) in the groups (Table III). The

infants in both the groups took more time in hospital than the older children. The duration of hospital stay of children who got all the 5 micronutrients, vitamin A and zinc was shorter than those children who got vitamin C, vitamin E and folic acid (Table IV). There was no difference in time of disappearance of fever and feeding difficulty. But fast breathing and chest indrawing disappeared earlier ($p<0.01$) in micronutrient group than control group (Table V).

Table III: Duration of hospital stay of control and intervention group (N=800)

Age group	Duration (Days)			
	Control group		Intervention group	
	No.	Duration	No.	Duration
Birth-1year	229	7.78	221	7.23
1-3 years	136	7.75	144	6.75
3-5 years	35	7.75	35	6.50
Total	400	7.75	400	6.75

$p<0.01$

Table IV: Duration of hospital stay of intervention group (N=400)

Number	Average duration (Days)
Who got 5 micronutrients (200)	6.05
Who got vitamin A (40)	6.50
Who got vitamin C (40)	7.00
Who got vitamin E (40)	7.00
Who got folic acid (40)	7.00
Who got zinc (40)	6.75

$p<0.05$

Table V: Effect of micronutrients on selected clinical signs

Signs	Duration of disappearance	
	Control group (Days)	Micronutrient group (Days)
Fever	2.0	2.0
Feeding difficulty	2.0	2.0
Fast breathing	4.5	4.0
Chest indrawing	3.5	3.0

$p<0.01$

Discussion

Among the children studied, 59.00%(475) were male and 41.0%(325) were female. The male female ratio was 1.4:1. A study conducted on children suffering from pneumonia in Dhaka Shishu Hospital showed male and female ratio as 2:1[34]. Two other studies[35,36] conducted abroad showed male and female ratio as 61:39 and 69:31 respectively in hospitalized children suffering from pneumonia. This may be due to the fact that male children in our society are given more care than female ones due to various reasons or male children actually suffer more from diseases than female ones[37]. The study shows that 56.25%(450) children were infants and the Mean±SD age was 6.5±5.6 months. One study conducted in our country has shown that ARI most commonly (84%) occurs in infancy followed by 1-4 years of age, which is consistent with the present study[38].

The individual values of the levels of micronutrients in the samples were either marginally normal or below the normal level. WHO estimates that about 2.70% pregnant women suffer from frank vitamin A deficiency with a vast number suffering from borderline deficiency in developing countries[39]. As a result, the fetuses get les nutrients in utero and are born with deficit of micronutrients. The rate of exclusive breast feeding was also low in the samples which resulted in getting less micronutrients. The non-breastfed children were also not properly weaned. Those weaned, the foods contained low amount of micronutrients. This may be also the cause of micronutrient deficiency[40]. Widespread micronutrient deficiency in preschool children and mothers has also been demonstrated in Nigeria where 40.00% of the boys had vitamin A deficiency and 47.00% had vitamin C deficiency[41]. In Nepal, there is widespread multiple micronutrient deficiency in pregnant women and 12.00-18.00% of the mothers suffer from night blindness during pregnancy[42,43].

The average duration of hospital stay of children in control group was 7.75 days and that of children in intervention group was 6.75 days. One study conducted in Brazil on children aged 6 months to 4 years has shown the duration of an episode in hospital as 6 days which is almost similar to the duration of this study[44]. Another case-control study in Brazil on efficacy of vitamin A treatment in non-

measles pneumonia has shown the average duration of an episode as 7.60 days in cases and 7.50 days[45]. Although the difference of one day may be very short but it is significant in the sense that discharge of a patient one day before the expected period saves resources of the hospital. Micronutrients enhance immune status and prevent tissue damage by antioxidant activity. They also exert enhanced regeneration of epithelium. As a result, morbidity is reduced and there is early recovery from the disease[46].

The duration of hospital stay of children who got all the 5 micronutrients was shorter than those children who got one micronutrient. As most of the children studied were malnourished and there were deficiencies of multiple micronutrients in these children, their immune status was probably very low. So, the children who got all the micronutrients, their immune status were probably improved to enhance the cure of the diseases than the children who got a single micronutrient. One study in Vietnam on 163 children of aged 6-24 months there was simultaneous low concentration of several micronutrients (haemoglobin, retinol and zinc) and after supplementation of micronutrients in these subjects, their micronutrient status were improved and took less time to be cured from acute infection which goes in favour of this study[47]. One review study has also described that micronutrient such as vitamin A and zinc given as a therapy may benefit the clinical course of childhood pneumonia[48]. Another study in Indonesia has shown that micronutrient supplementation in children improves the micronutrient status[49].

There was no difference in the mean number of days of disappearance of fever and feeding difficulty. But fast breathing and chest indrawing disappeared a bit earlier in intervention group. One study in Tanzania has shown that the average duration of hospital stay was 4.2 days and there was no difference of disappearance in the mean duration of fever in children suffering from pneumonia[50].

Conclusion

Every study has some weaknesses and constraints. Micronutrient levels were done only before starting of treatment. They were not done at the end of the treatment due to economic constraints, which could be helpful to see the difference between the serum levels of micronutrients. Vacutainer test tubes were not used to draw blood which is ideal to prevent the contamination with air. Blinding of the samples has not been done which could increase the quality of the study. If tissue levels of micronutrients could be done, it could reflect the actual micronutrient status in the samples. In spite of these constraints, the results reveals that micronutrient deficiency is abundant among children of Bangladesh especially among under-five children in the northern zone of country and micronutrient supplementation may be beneficial as an adjunct to specific antimicrobial therapy among hospitalized children suffering from pneumonia.

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