Effect of micronutrients on morbidity and duration of hospital stay in childhood pneumonia

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Abstract
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 8 children died, 100 children left the hospital on `Risk Bond', 190 children were discharged `On Request' of the parents before cure, 8 children developed various complications and 44 children had other factors to be excluded from the study. Finally data from 800 children were analyzed. Among these 800 children 59.00% were male and 41.00% were female. The mean ± SD age was 6.5±5.6 months and 56.25% 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-group. All the samples were suffering clinically from severe pneumonia and radiologically from bronchopneumonia. Cases and controls were matched by parents' occupation (fathers were cultivators and mothers were housewives), education level (up to primary level), economic status (having no deficit or surplus of products) and family members (five in number). All the children were fully vaccinated as per existing EPI schedule of the country, partially fed by breastmilk and infant formula 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 vitamin A (retinol), vitamin C, vitamin E, folic acid and zinc from all the samples before starting treatment by standard procedures. The individual values of level of micronutrients in the samples were either low or marginally normal but the average level of all the values were low. The average duration of hospital staying was 6.75 days in intervention group and 7.75 days in control group. Chest indrawing and fast breathing disappeared earlier in the intervention group suggesting that supplementation of micronutrients decrease the morbidity and duration of hospital stay of children suffering from pneumonia.

Keywords
Micronutrient supplementation, morbidity from pneumonia, hospital stay.

Introduction
At present situation, 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.1,4 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 remains 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 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 various 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.6,7,8 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.

Materials and methods
The study was a cross-sectional, prospective
and controlled micronutrient supplementation
trial. The trial enrolled children admitted to
the hospital with pneumonia. The selected
place of study was the Paediatics Department
of Rangpur Medical College Hospital. The
study was conducted 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.
Among these, children having the clinical
diagnosis of severe pneumonia and
radiological diagnosis of bronchopneumonia
on admission were selected as samples. The
duration of hospital stay was calculated in a
quantitative form and it is a continuous
variable and the statistical formula 4σ²/L² 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.20-22 In this way, the
optimum number of samples became 384.
This was rounded to 400. Since there were
two independent groups, double the optimum
number (400x2=800) was selected as
samples. 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 of the child, educational status of the
parents, monthly family income of the
parents, breast feeding pattern, time and type
of weaning foods offered to the child,
immunization status of the child, vitamin A
supplementation, vitamin C supplementation,
vitamin E supplementation, supplementation
of folic acid, supplementation of zinc etc.
Anthropometric index such as weight was
included in the questionnaire to obtain
nutritional status. 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 from the selected study population. 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. Age was recorded from the memory of the mothers or from the birth certificates or immunization cards. Educational status of the parents was determined by direct question to the mother or attendant. Only those who had formal schooling were considered literate and those parents who had only education up to primary level were included. Occupation of the parents and amount of the monthly income was also determined by direct question to the mother. Only those fathers who were cultivators and mothers who were housewives and who had no deficit or no savings of products were under consideration. Status of breast feeding and daily food intake was collected from the memory of the mother. The children who were partially breastfed (taking breastmilk as well as other milks up to six months) and taking carbohydrate rich weaning foods after six months were included. During examination `the Bar Scale' designed by National Nutritional Council of Bangladesh was used to record the body weight. The balance was checked everyday before use and weight was recorded on bare foot and with light clothes. The children who received all the vaccines according to the existing EPI schedule was regarded fully vaccinated. All the questionnaires were filled by the investigator himself.

The children who left the hospital on `risk bond' or were `absconded' form the ward after admission or `expired' during treatment were excluded from the analysis. Also those who developed a complication such as effusion, collapse, pneumothorax etc. and who were suffering from bronchial asthma and other severe systemic diseases with pneumonia were excluded from the study. The children who required antibiotics other than the ampicillin and gentamycin for cure were also excluded from the study. The children 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 from the study. Data were collected from 1150 children. Among them 8 children died, 100 children left the hospital on `Risk Bond', 190 children were discharged `On Request' of the parents before cure, 8 children developed various complications and 44 children had other factors to be excluded from the study. Finally data from 800 children were analyzed.

Answers of the mothers and findings of clinical examinations were recorded in the pre-tested and prepared "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 the estimation of serum level of vitamin A (retinol), vitamin C (ascorbic acid), vitamin E, folic acid and zinc. The method of analysis was High Performance Liquid Chromatography (HPLC)\textsuperscript{23-28} for vitamin A, vitamin C, vitamin E, colorimetric method for zinc\textsuperscript{29,30} and ELISA\textsuperscript{31} for folic acid. The selected laboratories were Padma Diagnostic Center, Dhaka and Apollo Diagnostic Center, Rangpur. Tests were performed by skilled laboratory technologists trained in that field and checked 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 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 five groups (200+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.

Micronutrients were also given to the intervention group. The brands were selected from the products of reputed pharmaceutical companies. The doses of (a) vitamin A was 50,000 or 100,000 IU (age under 1 year) and 100,000-200,000 IU (age over 1 year), (b) vitamin C 125 mg daily, (c) vitamin E 40 IU daily, (d) folic acid 2.5 mg daily and (e) zinc 10.0 mg daily. In 200 children, all the 5 micronutrients were given and another 200 children were divided into 5 sub-groups (40 in each sub-group) and in each sub-group only one micronutrient was prescribed along with specific treatment. 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.

There is no formal ethical committee in the hospital. Written permission was taken from the Director of the hospital and from the head of the department of Paediatrics to conduct the study in the ward. Then purpose of the study was explained to the parents. Then after having the consent, each child was included in the study maintaining the principles of Helsinki Declaration\textsuperscript{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. Data were presented in simple and compound tables. The data were arranged according to the age group, micronutrient group and control group. The micronutrient group was also rearranged into single micronutrient group and all micronutrient groups.

### Results

Among 800 children studied 56.25% (450) were infants (up to 1 year), 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. Children of the infancy period were most sufferers from pneumonia. Among the above children 59.00% (475) were male and 41.00% (325) were female. The mean±SD age was 6.5±5.6 months (Table 1). The average serum level of vitamin A (retinol) was 0.60 µmol/l, vitamin C (ascorbic acid) was 32.50 µmol/l, vitamin E was 6.50 µmol/l, folic acid was 3.50 nmol/l and the average serum level of zinc was 9.70 µmol/l. The average serum level of all the micronutrients considered was lower than the normal level (Table 2).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Sex of the children</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (%)</td>
<td>Female (%)</td>
</tr>
<tr>
<td>Birth-1-year</td>
<td>255 (31.88)</td>
<td>195 (24.37)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>105 (13.12)</td>
<td>85 (10.62)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>65 (8.12)</td>
<td>25 (3.12)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>35 (4.37)</td>
<td>15 (1.88)</td>
</tr>
<tr>
<td>4-5 years</td>
<td>15 (1.88)</td>
<td>05 (0.63)</td>
</tr>
<tr>
<td>Total</td>
<td>475(59.00)</td>
<td>325(41.00)</td>
</tr>
</tbody>
</table>

(Mean age ± SD = 6.5 ± 5.6 months)

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. Again the neonates in both the groups took more time in hospital than the older children.
Table 2: Average baseline serum concentrations of micronutrients in the samples (n=800)

<table>
<thead>
<tr>
<th>Item</th>
<th>Average (serum) level ± SD</th>
<th>Normal value</th>
<th>Difference from lowest mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>0.60 ± 0.05µmmol/l</td>
<td>0.70-1.50µmmol/l</td>
<td>0.10 µmol/l</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>32.50±0.15µmmol/l</td>
<td>34.00-113.00 mmol/l</td>
<td>1.50 µmol/l</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>6.50 ± 0.45µmmol/l</td>
<td>7.00-21.00 mmol/l</td>
<td>0.50 µmol/l</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>3.50 ± 0.04 nmol/l</td>
<td>4.10-20.40 nmol/l</td>
<td>0.60 nmol/l</td>
</tr>
<tr>
<td>Zinc</td>
<td>9.70 ± 0.74µmmol/l</td>
<td>9.8-18.1µmmol/l</td>
<td>0.10µmol/l</td>
</tr>
</tbody>
</table>

(ANOVA P<0.10)

The average difference was 12.90% (1.0 day) in the groups (Table 3). 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 4). There was no difference in time of disappearance of fever and feeding difficulty. But fast breathing and chest indrawing disappeared earlier in micronutrient group than control group (Table 5).

Table 3: Duration of hospital stay of control and intervention group (N=800)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Control group</th>
<th>Intervention group</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-1 year</td>
<td>229 7.78</td>
<td>221 7.23</td>
<td>0.55 (6.55)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>94 7.75</td>
<td>96 6.75</td>
<td>1.0 (12.90)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>42 7.75</td>
<td>48 6.75</td>
<td>1.0 (12.90)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>33 7.75</td>
<td>27 6.75</td>
<td>1.0 (12.90)</td>
</tr>
<tr>
<td>4-5 years</td>
<td>12 7.74</td>
<td>8 6.25</td>
<td>1.49 (19.25)</td>
</tr>
<tr>
<td>Total</td>
<td>400 7.75</td>
<td>400 6.75</td>
<td>1.0 (12.90)</td>
</tr>
</tbody>
</table>

Table 4: Duration of hospital stay of intervention group (N=400)

<table>
<thead>
<tr>
<th>Number</th>
<th>Average duration (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who got 5 micronutrients (200)</td>
<td>6.05</td>
</tr>
<tr>
<td>Who got vitamin A (40)</td>
<td>6.50</td>
</tr>
<tr>
<td>Who got vitamin C (40)</td>
<td>7.00</td>
</tr>
<tr>
<td>Who got vitamin E (40)</td>
<td>7.00</td>
</tr>
<tr>
<td>Who got folic acid (40)</td>
<td>7.00</td>
</tr>
<tr>
<td>Who got zinc (40)</td>
<td>6.75</td>
</tr>
</tbody>
</table>

Table 5: Effect of micronutrients on selected clinical signs

<table>
<thead>
<tr>
<th>Signs</th>
<th>Duration of disappearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (Days)</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Feeding difficulty</td>
<td>2</td>
</tr>
<tr>
<td>Fast breathing</td>
<td>4.5</td>
</tr>
<tr>
<td>Chest indrawing</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Discussion

Among the children studied, 59.00% (475) were male and 41.0% (325) were females. The male female ratio was 1.4:1. A study conducted on children suffering from pneumonia in Dhaka Shishu (children) Hospital showed male and female ratio as 2:1. Two other studies 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. 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.

The individual values of the levels of micronutrients in the samples were either marginally normal or below the normal level but the average serum level of all the micronutrients considered were lower than the normal level. There may be several reasons behind this. Bangladesh is a country of widespread micronutrient deficiency. The mothers and children are number one victim of micronutrient deficiency. 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. As a result, the fetuses get less nutrients in utero and are born with deficit of micronutrients. The rate of exclusive breast feeding is also low. So, the breastfed children get less micronutrients. The non-breastfed children are also not properly weaned. Those weaned, the foods contain low amount of micronutrients. They also suffer from micronutrient deficiency. Widespread micronutrient deficiency in preschool children and mothers has also been demonstrated in studies conducted in other places. In Nigeria, 40.00% of the boys had vitamin A deficiency and 47.00% had vitamin C deficiency. 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. There may be other factors for the lower values of micronutrients in this study. Fever or physical stress associated with acute infection can deplete the body stores of vitamin A or can increase the urinary loss of vitamin A. Oxidative stress in infection can also decrease the level of anti-oxidant micronutrients. But in these cases, the major clinical features were respiratory distress and many of the children did not require oxygen therapy which may be suggestive that the deficiencies were mainly due to dietary causes.

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. The difference is statistically not very significant but the cumulative difference of 1.0 day for 400 cases (addition of differences) over the year is very important for a hospital. 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. 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 in the control group which was not statistically very much significant but the cumulative difference of 0.10 day for a hospital was significant. 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. But micronutrients take time to initiate full physiological function. Because, after administration of any micronutrient, at first, there is accumulation in the storage site, then there is increase in the serum level, then tissue binding through specific receptors and the exertion of physiological activity. So, immediately after administration of a micronutrient, there may no much difference in the period of morbidity as was in this study.

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

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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. 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. Another study in Indonesia has shown that micronutrient supplementation in children improves the micronutrient status. In the hospital, 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 micronutrient 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.

Conclusion
Every study has some weaknesses and constraints which is not an exception in this study. 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. After centrifugation and separation, the serum was kept in the refrigerator. Occasionally there was interference of supply of electricity. This may have some effect in the biochemical values of the micronutrients. There was difficulty in taking dietary history. It was very difficult to explore the monthly income of the parents, because there was no record of the income in the families. In some cases, there was tendency of by-passing to disclose the actual income. 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, this study documents the effectiveness of micronutrient supplementation as an adjunct to specific antimicrobial therapy among hospitalized children suffering from pneumonia. It may be concluded that micronutrient deficiency is abundant among children of Bangladesh especially among under-five children in the northern zone of country. The economic status of the people of this zone is poor which may contribute the situation. Micronutrients should be given routinely to all children suffering from pneumonia to reduce both public and private cost by reducing the duration of hospital stay.

References
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