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Original Research Article

Nutrient deficiencies (Copper, Zinc, Iron, Magnesium) among children with SIRS/sepsis-a hospital based cross sectional study

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ABSTRACT

Background: In developing countries sepsis is a major etiological factor contributing to 60-80 % of annual mortality. SIRS/sepsis rates are high among children admitted to hospitals particularly in intensive care units. Oxidative stress plays important role in etio-pathogenesis of SIRS/sepsis. Nutrients with antioxidant activity enhance immune system there by decreasing severity of SIRS/sepsis. Estimation of such nutrient levels might establish relationship with oxidative stress in children with SIRS/sepsis.
Methods: A hospital based cross-sectional study was done on consecutive samples of 96 children diagnosed with SIRS/sepsis. Serum copper, iron zinc, magnesium levels of children diagnosed with sepsis/SIRS included in the study were estimated, data were represented as median with inter quartile range and proportions. Mann Whitney u test and Karl Pearson's correlation tests were used to see correlation between clinical paramaters.
Results: Zinc and magnesium deficiency were seen in 68.8% and 59.4% children with SIRS/sepsis. Median serum magnesium levels were 1.24mg/dL in children with illness <1 week and 1.51mg/dL with illness >1week duration prior to hospitalization (p=0.017). Hospital acquired infections were higher with zinc (P=0.001) and copper deficiency(P=0.002). Zinc deficiency correlated with need for longer hospitalization (P= 0.017). Mortality due to SIRS/sepsis increased as number of nutrient deficiencies increased (P =0.009).
Conclusions: Significant number of children with SIRS/sepsis had nutrient deficiencies. These deficiencies correlated significantly with duration of illness prior to hospitalization. Children with nutrient deficiency had higher incidence of hospital acquired infections. Children with normal nutrient levels have decreased length of hospitalization. Children with multiple nutrient deficiency had higher risk of death.

Keywords: Nutrient deficiency, Oxidative stress, Sepsis, Systemic inflammatory response syndrome

INTRODUCTION

Prevalence of Systemic Inflammatory Response Syndrome is high among hospitalized children and risk of these children developing sepsis is considerably high.[1] Global incidence of sepsis is increasing and it affects about 18 million children every year.[2] Children surviving sepsis have twice the risk of death in subsequent 5 years as compared with hospitalized controls without sepsis and they also suffer from non-infective health problems.[3]

Nutrients are components in food that are used for survival and growth. Childhood is a stage of rapid physical development during which large amounts of trace elements are needed not only for maintenance but also for growth. Nutrients like copper, iron, zinc, magnesium limit mitochondrial dysfunction which occurs due to imbalance between reactive oxygen species and antioxidants seen in SIRS/sepsis.[4] These nutrient levels in serum decrease in infections as they utilized for production of antibodies, acute phase reactants,

compliment.[5] Such nutrients levels in the body particularly with antioxidant activity are susceptible to pathological conditions.[6] With increasing severity of SIRS/ sepsis, there will be larger depletion of antioxidants.[7] Manzanares W et al in their meta-analysis concluded that supplementation of trace elements and vitamins with antioxidant activity improves outcome.[8]

Despite the effect of SIRS on different nutrients is known, it is not translated into routine clinical practice for management of SIRS/sepsis.[9] Present study was carried out to study profile and magnitude of nutrient (copper, iron, zinc, magnesium) deficiency, effect of duration of illness on nutrient levels, role of their deficiency in hospital acquired infections and outcome in children diagnosed with SIRS/sepsis with associated deficiency of nutrients.

METHODS

This was a cross-sectional study conducted from October 2013 to September 2015 at-Regional Advanced Pediatric Care Center (RAPCC) and Kasturba medical college and hospital, Manipal university, Manglore. Ninety-six children clinically diagnosed with SIRS/sepsis of age between 1 to 16 years were included in our study. Children were diagnosed with SIRS/sepsis as per diagnostic criteria defined by international consensus conference on pediatric sepsis and organ dysfunction. Those children with diseases that affect the immune system, genetic diseases related to metabolism of nutrients were excluded from our study.

Sample size was calculated as 96 based on a previous study and anticipated nutrient deficiency among children with SIRS/sepsis was taken as 39% with 95% confidence interval.[9] Subjects were recruited into our study after necessary permissions were taken from institutional ethics committee, consents from parents/care givers and assent from included subjects were obtained. Data was documented using structured proforma following which non-fasting blood samples were taken for analysis of nutrients (copper, zinc, iron, magnesium) soon after recruitment into study. The serum was separated and stored at-20 degree centigrade for analysis. Nutrient levels were estimated by Nitro PAPS end point method, Quantitative colorimetric determination at 354nm, Colorimetric assay using ferrozyme, Xylidyl blue endpoint method, colorimetric method using star 21 semi autoanalyser for zinc, copper, iron and magnesium respectively.

SPSS version 15 was used for statistical analysis. Results were presented as median with inter quartile range for baseline characteristics and as proportions for nutrient status. Comparision of groups were done using mann whitney u test, Pearson's correlation test. P value of less than 0.05 was considered as statistically significant.

RESULTS

Our study included a total of 96 children of which 69 children had SIRS and 27 had sepsis. Of this total population, irrespective of SIRS group or sepsis group the proportion of children who had deficiency of zinc and magnesium was high which was 68.8% and 59.4%. However, the median serum values of nutrients did not vary significantly between SIRS and sepsis groups. Proportion of children with copper, zinc and iron deficiency increased as duration of illness prior to hospitalization was more but statistical significance was noted for iron with p value of 0.015. Median serum levels of magnesium were significantly low in children with prolonged duration of illness prior to hospitalization, this was statistically significant with P value of 0.017 as described in Table 1.

Table 1: Relation between duration of illness prior to hospitalization and nutrient status.

Duration of illness	Proportion of Deficiency	Percentage (%) of deficiency	Median levels of the deficient population in mcg/dl	Inter quartile range Q25-Q75	P value
Copper					
< 1week	12/62	19.4%	134.0	86.5-162.67	
≥ 1 week	10/34	29.4%	124.70	83.51-159.65	0.946
Zinc					
< 1week	40/62	64.5%	42.1250	16.18- 69.62	
≥ 1 week	26/34	76.5%	56.5350	75.10 – 14.31	0.395
Iron					
< 1week	3 /62	4.8%	51.6950	36.64- 86.21	
≥ 1 week	8/34	23.5%	58.2300	37.76-102.47	0.212
Magnesium					
< 1week	37/62	59.7%	1.51	0.93-2.05	
≥ 1 week	20/34	58.8%	1.24	0.53-1.71	0.017

Correlation of nutrient deficiency with duration of hospital stay was studied. There were high proportion of children with magnesium, iron and copper deficiencies with prolonged hospitalization but it was not significant

statistically. Children with low serum zinc levels at admission were observed to have longer hospitalization with statistically significant P value of 0.017 as described in Table 2.

Table 2: Relation between duration of hospital stay and nutrient levels.

Duration of hospital stay	Proportion (n)	Percentage (%) of deficiency	Median in mcg/dl	Inter quartile range Q25-Q75	P value
Copper					
< 2week	4/36	11.1%	131.7500	92.45-165.72	
≥ 2 week	18/60	30%	135.4428	70.26-158.38	0.340
Zinc					
< 2week	21/36	58.3%	33.7100	21.78-96.90	
≥ 2 week	45/60	75%	65.1950	14.05-67.49	0.017
Iron					
< 2week	5/36	13.9%	52.7000	37.57-89.28	
≥ 2 week	6/60	10%	53.8500	36.92-92.25	0.658
Magnesium					
< 2week	20/36	55.6%	1.137650	0.84-1.79	
≥ 2 week	37/60	61.7%	1.30400	0.52-1.89	0.552

Median serum values of nutrients in study population with hospital and community acquired infections were compared. All the nutrients (copper, zinc, iron and magnesium) were low in children who were grouped into hospital acquired infections which was statistically significant for copper and zinc with P value of 0.001 and 0.002 respectively as described in Table 3.

Table 3: Relation between source of infection and nutrient status.

Source	Proportion	Percentage (%) of deficiency	Median in mcg/dl	Inter quartile range Q25-Q75	P value
Copper					
Hospital	2/11	18.2%	70.2600	42.70-87.80	0.001
Community	20/85	23.5%	135.700	92.51-164.50	
Zinc					
Hospital	9/11	81.8%	53.2100	5.23-18.68	0.002
Community	57/85	67.7%	134.500	17.31-73.66	
Iron					
Hospital	1/11	9.1%	49.3300	34.09-64.99	0.186
Community	10/85	11..8%	53.7000	37.23-94.84	
Magnesium					
Hospital	7/11	63.6%	0.70200	0.52-1.62	0.320
Community	50/85	58.8%	1.345	0.73-1.87	

Table 4: Relation of outcome with nutrient status.

Element	Number of children with deficiency	Percentage (%) of deficiency	Percentage of deficiency in		P	Correlation coefficient R
			outcome recovered	outcome death		
Copper	22	22.9	21.7%	50%	0.472	-0.074
Zinc	66	68.8	93.9%	100%	0.061	-0.192
Iron	11	11.5	9.8%	50%	0.064	-0.190
Magnesium	57	59.4	58.7%	75%	0.466	-0.075

In the study population 4 children had mortality and all the 4 had zinc deficiency. All the 4 also had more than one nutrient deficiency. There was a negative correlation between nutrient levels and outcome of subjects as

described in Table 4. There was a positive correlation between number of nutrients that the children were deficient in and their outcome which was statistically significant with P value of 0.009 and Pearson's correlation coefficient was 0.236 as described in Table 5.

Table 5: Relation of multiple nutrient deficiency with outcome.

Number of nutrients in which deficiency was seen	Number in each group n (%)	Outcome			P value	Correlation coefficient
		Recovered n (%)	Partially recovered n (%)	Death n (%)		
0	16(16.7)	15(93.8)	1(6.2)	0(0)	0.009	0.236
1	27(28.1)	23(85.2)	4(14.8)	0(0)		
2	34(35.4)	34(88.2)	3(8.8)	1(2.9)		
3	15(15.6)	10(66.7)	2(13.3)	3(20)		
4	4(4.2)	2(50)	2(50)	0(0)		

DISCUSSION

Sepsis is a significant health problem and is one of the leading causes of morbidity and mortality in the children The incidence of the sepsis syndromes has increased over the last three decades significantly, with increasing mortality occurring in spite of decline in overall hospital deaths.[10] Special Care Units do not consider the effects of SIRS/sepsis on the concentrations of trace elements, there are no specific guidelines which have been developed on how these plasma concentrations should be interpreted in the presence of a SIRS. There is need for more studies to assess the effects of different types of nutrients and their doses for supplementation in children with different types of critical illness.[5] Laboratory monitoring of nutrient levels is an important part of the assessment and management of all patients receiving nutritional support.[8] This study was aimed at estimating the concentrations of elements which have immune- protective role like copper, zinc, iron and magnesium in children diagnosed with SIRS/sepsis.

Proportion of children with deficiencies of copper, zinc, and magnesium were higher in children in sepsis group when compared to SIRS group. Similar observation is seen study by Talwar D et al where children with high CRP levels had lower levels of different nutrients and vitamins. Which shows with severe disease children are more prone for nutrient deficiencies.[9]

Serum copper levels in our study was normal to high in most of the children which was similar to the study done by Angelova M et al and Wang G et al which can be due elevated ceruloplasmin during inflammatory process.[11,6] Contrary to this Djoko KY et al in their study showed that copper levels were low in sepsis and deficient subjects had more morbidity due to infections and worse prognosis.[12]

Serum zinc levels were low in majority of patients which was similar to studies done by Djoko KY et al, Wang G et al.[12,6] This evidence is further supported by a study by, Srinivasan MG in which subjects supplemented with zinc had less infections.[13] In contrary to this study done by Duncan A et al in their study demonstrated that zinc supplementation has no role in preventing infections.[14]

Serum iron levels were normal in majority of the subjects which could be due to elevated ferritin which is an acute phase reactant. Contrary to this, in studies done by Wang G et al, Djoko KY et al, Bresnahan K serum iron levels were low in children with sepsis.[6,12,15]

Serum magnesium levels of children were low in greater proportion proportion of children similar to study by Cojocaru IM et al were children with acute infections had low serum magnesium values but there was no correlation found with severity of the disease. Similar observations were seen in study by Tam M et al.[16,17]

Children with prolonged duration of illness prior to diagnosis had higher proportion of deficiencies of copper, zinc and iron, with median serum level significant for magnesium which can be due to severity of the disease or more sequestration of these nutrients for immune function as postulated by Visser J et al.[5]

Proportion of children with deficiencies of copper, zinc, magnesium increased and median serum zinc value was significantly low in children with prolonged hospital stay. Results were similar to study done Mehta N et al where children had prolonged duration of hospital stay with multiple nutrient deficiencies.[18] In our study, we observed children with normal nutrient status had faster recovery.

Median serum values all the nutrients were low with statistical significance for copper and zinc in children who had hospital acquired infections. There are no prior studies on relationship of nutrient status and hospital acquired infections.

Children with complete recovery had less nutrient deficiency. This observation was similar to the study done by Comstedt P et al where 28-day mortality was high in children who had SIRS at admission to the

hospital, and dhabi et al where length of hospital stay was less in children supplemented with micronutrients.[19,20]

Children with multiple nutrient deficiencies had higher mortality. This was a novel observation in our study with no previous studies relating number of nutrient deficient and outcome of patients diagnosed with SIRS/ sepsis.

In our study cause-effect relationship could not be determined, nutrient levels prior to infection were not known. Further longitudinal studies are warranted to ascertain these results and to establish a cause- effect relationship. Studies estimating serum levels in same patient during different stages of the disease would help to know how their levels behave in the disease processes. Randomised controlled trials and supplementation studies would be valuable in verifying the utility of supplements in preventing SIRS and its progression to sepsis. Community based studies to see weather zinc and copper fortification can decrease hospital acquired infections are warranted.

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