Original Article

장기간 정맥 영양 의존적 신생아에서의 구리 결핍 현황과 공급 평가

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Copper Deficiency and Evaluation in Infants Requiring Long-term Parenteral Nutrition

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Background : Long-term parenteral nutrition (PN) can increase the risk of copper deficiency. This study aimed to analyze the incidence and risk factors associated with copper deficiency in infants requiring long-term PN and to evaluate the adequacy of intravenous (IV) copper supplementation.

Methods : This was a retrospective study of infants who were admitted to the neonatal intensive care unit (NICU) of a tertiary hospital in Korea from July of 2015 to June of 2020, had their serum copper concentration measured, and received PN for more than two weeks. Patients who were supplemented with IV copper and whose serum copper concentration was monitored after administration were placed in a subgroup to evaluate the copper supplementation.

Results : Of the 63 patients, 39 (61.9%) were deficient in copper (serum Cu <70 µg/dL). In the copper deficiency group, gestational age and birth weight were significantly lower, and the proportion of premature infants and extremely low-birth-weight infants were significantly

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higher. Gestational age of less than 32 weeks was an independent risk factor for copper deficiency. In the copper deficiency group, the total NICU stay was longer, absolute neutrophil count, hemoglobin, and platelet levels were lower, and the proportion of bronchopulmonary dysplasia and rickets was higher.

Conclusion : Copper deficiency was common in infants receiving long-term PN without copper, especially in patients of young gestational age. Adequate copper supplements are recommended to prevent the clinical consequences of copper deficiency. It is necessary to develop single-entity products of IV copper or multi-trace element products suitable for infants.

[Key words] Copper; Infant, Newborn; Intensive Care Units, Neonatal; Parenteral Nutrition; Supplementation

Copper is an essential trace element and a functional component of several enzymes, including cytochrome oxidase, superoxide dismutase, monoamine oxidase, and lysyl oxidase.¹⁾ Copper plays an essential role in connective tissue formation, iron metabolism, hematopoiesis, and central nervous system function. Although copper deficiency is rare, it has been reported in patients with severe malabsorption, premature infants, children recovering from severe malnutrition, and patients receiving parenteral nutrition (PN) without copper supplementation.²⁾ Manifestations of copper deficiency include pancytopenia, bone abnormalities, myocardial diseases, depigmentation of skin and hair, and neurologic abnormalities.^{3),4)} Severe copper deficiency is associated with anemia, neutropenia, thrombocytopenia, and osteoporosis. Risk factors for copper deficiency include low birth weight, inappropriate intake, prolonged diarrhea, and malabsorption.^{5),6)} There is an increased risk of copper deficiency in premature infants because most copper accumulation occurs during the third trimester of pregnancy.^{7),8)}

Copper is absorbed in the stomach and the small intestines by enterocytes in the duodenum.^{9),10)} Patients with chronic gastrointestinal disease may have reduced copper absorption, resulting in copper deficiency. Copper is excreted primarily by the liver into the biliary system under normal physiologic conditions.¹⁰⁾ It has conventionally been recommended to exclude copper from PN in patients with cholestasis. However, recent studies suggest that this may lead to copper deficiency. Supplying copper through PN and monitoring serum copper concentration is now recommended.¹⁰⁾⁻¹³⁾

Long-term PN can result in copper deficiency. In a retrospective study of hospitalized pediatric patients receiving PN in the United States, 71% of the patients not supplemented with copper and 50% of the patients supplemented with copper had low serum copper levels of less than 75 µg/dL.⁷⁾

The 2005 American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend providing trace elements, including copper, from PN initiation, and the recommended intake of copper in infants is

20 µg/kg/day.¹⁴⁾ Likewise, the 2005 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommended that 20 µg/kg/day of copper be supplied to parenterally fed infants and children. However, the revised 2018 guidelines recommend that the copper intake be increased to 40 µg/kg/day in premature infants and 20 µg/kg/day (max. 0.5 mg/day) for term infants.¹⁾ It is also recommended that plasma copper levels and ceruloplasmin be monitored in patients on long-term PN.

At the neonatal intensive care unit (NICU) of our hospital, infants receive PN which does not contain copper in the beginning, and serum copper concentration is monitored if the PN is maintained longer than 4 weeks. When copper is deficient, infants receive 10~20 µg/kg/day of copper as multi-trace element formulations. Serum copper concentration is monitored on a monthly basis during PN. The amount of copper is adjusted based on the patient's serum concentrations of copper and other trace elements. However, there are several limitations in copper supplementation through PN. Since single-entity intravenous (IV) copper products are not available in Korea, IV copper should be supplemented with only multi-trace element products. The composition of such products is often not suitable for infants, resulting in an unmet supply of each trace element. Neonatal multi-trace element preparations can provide trace elements in amounts closer to the requirements in neonates. However, other trace elements, such as manganese and chromium, make it still difficult to supply copper at the recommended doses. Also, its expensive cost is not covered by national health insurance.

There is a lack of research on copper sup-

plementation in long-term PN patients in Korea, especially on copper deficiency and evaluation of IV copper supplementation in infants. This study aimed to analyze the incidence of and risk factors for copper deficiency and evaluate IV copper supplementation in infants requiring long-term PN. This research can help to prevent copper deficiency in infants.

METHODS

1. Research subjects

We included patients who were admitted to the NICU of our hospital from July of 2015 to June of 2020, had their serum copper concentration measured at least once during their hospital stay, and received PN for more than two weeks in this study. Patients were divided into a deficient group (with a serum copper concentration of <70 µg/dL) and a non-deficient group (with a serum copper concentration of ≥70 µg/dL) based on their serum copper concentrations.¹⁵⁾ Serum copper concentration was defined as the first measured value after admission to the NICU. Patients who were given copper before the first copper concentration measurement and patients for whom we lacked basic information, such as gestational age, were excluded (Fig. 1). Subgroup analysis was conducted on patients who were administered the multi-trace element products [SciGen NeoTrace 4 Injection (Pediatric) (Daehan New Pharm, Seoul, Korea) or Furtman Inj 2 ml (JW Pharmaceutical, Seoul, Korea)], and had their serum copper concentrations measured before and after administration. Patients who were administered IV copper for less than two weeks and those whose serum copper

Fig. 1 Subject selection algorithm

concentration was measured more than one month after discontinuing IV copper administration were excluded from the subgroup analysis. This study was conducted under the approval of the Institutional Review Board of Seoul National University Hospital, and consent from the study subjects was exempted due to the retrospective nature of the study (IRB no. H-2008-149-1151).

2. Data collection

We retrospectively reviewed the electronic medical records of patients from the time of admission to the time of discharge. We investigated basic characteristics such as gestational age, prematurity, birth weight,

small for gestational age, extremely low birth weight infants, one-minute and five-minute Apgar score, gender, mode of delivery, and multiple birth as well as serum copper concentrations, IV copper administration, and IV copper formulations. We also examined nutritional characteristics, such as PN duration, type and amount of enteral nutrition, and amount of calories supplied by PN. We collected data on clinical characteristics including total hospital stay, total NICU stay, stage 2 or higher necrotizing enterocolitis, gastrointestinal surgery, stomy, cholestasis, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), rickets and patent ductus arteriosus requiring treatment (medication or surgery). Clin-

ical information was also collected, including the absolute neutrophil count (ANC), hemoglobin levels, platelet count, high sensitivity C-reactive protein (hs-CRP) levels on the closest day before the first serum copper concentration measurement.

Patients were evaluated for copper deficiency based on their first measured serum copper concentration during their hospital stay. We analyzed the differences in basic, clinical, and nutritional characteristics, complete blood cell count, and clinical results depending on copper deficiency and the risk factors for copper deficiency.

In the subgroup analysis, we compared serum copper concentrations before and after copper administration. We analyzed the average dosage of IV copper supplementation ($\mu\text{g}/\text{kg}/\text{day}$) and changes in serum copper concentration. Copper concentration before supplementation was the value measured on the day closest to the beginning of IV copper administration, and copper concentration after supplementation was the value measured on the closest day before the end of IV copper administration.

3. Statistical analysis

In the basic, clinical, and nutritional characteristics of the patients, continuous variables were compared by the t-test and categorical variables were compared by Chi-square test or Fisher's exact test. Continuous variable results were expressed as mean $\pm$ standard deviation, and categorical variable results were expressed as a frequency (%). Multivariate analysis was used to analyze the risk factors for copper deficiency. In the subgroup analysis, the concentrations before and after IV copper administration were

compared by paired t-test.

For statistical analysis, we used IBM SPSS Statistics ver. 25.0 (IBM Corp., Armonk, NY, USA), and a p-value of less than 0.05 was statistically significant.

RESULTS

1. Research subjects

1) Basic characteristics

A total of 76 patients who were admitted to the NICU of our hospital from July of 2015 to June of 2020 had their serum copper concentration measured at least once during their hospital stay. Among them, a total of 67 patients received PN for two weeks or more during their hospital stay. Of these, a total of 63 patients were included in this study, excluding the four patients who met the exclusion criteria. Of the 63 patients, 39 (61.9%) had a copper deficiency and 24 patients (38.1%) did not. A comparison of the patients' basic characteristics showed that gestational age ($p=0.004$) and birth weight ($p=0.007$) were significantly lower and the proportion of preterm infants ($p=0.02$) and extremely low birth weight infants ($p=0.035$) significantly higher in the copper deficiency group (Table 1). A gestational age of less than 32 weeks was an independent risk factor for copper deficiency (OR=6.192; 95% CI 1.057-36.264; $p=0.043$) (Table 2).

2) Clinical and nutritional characteristics

Serum copper concentrations were measured at 66.2 ± 41.9 days of postnatal age and 40.9 ± 6.6 weeks of postmenstrual age in total patients. Serum copper concentration ($\mu\text{g}/\text{dL}$) was significantly different between the two groups: 44.6 ± 14.2 in the copper-de-

Table 1 Basic demographics and characteristics

Characteristics	Total (n=63)	Cu deficient [†] (n=39)	Cu non-deficient [‡] (n=24)	P-value
GA, weeks	31.6±5.4	30.1±4.8	34.0±5.5	0.004*
Preterm [§] , n (%)	47 (74.6)	33 (84.6)	14 (58.3)	0.020*
Birth weight, kg	1.56±0.99	1.28±0.84	2.00±1.06	0.007*
SGA , n (%)	23 (36.5)	15 (38.5)	8 (33.3)	0.681
ELBW [¶] , n (%)	29 (46.0)	22 (56.4)	7 (29.2)	0.035*
1 min Apgar score (n=37/20)	4.3±2.3	3.9±1.9	5.2±2.6	0.056
5 min Apgar score (n=37/20)	6.6±1.9	6.3±2.0	7.3±1.7	0.054
Male, n (%)	30 (47.6)	22 (56.4)	8 (33.3)	0.075
Delivery (CS**), n (%)	46 (73.0)	30 (76.9)	16 (66.7)	0.373
Multiple births, n (%) (n=38/21)	18 (30.5)	13 (34.2)	5 (23.8)	0.406

Values are presented as mean±SD, or number (%)

*p <0.05

[†]Serum copper concentration <70 µg/dL

[‡]Serum copper concentration ≥70 µg/dL

[§]GA(gestational age)<37 weeks

^{||}Small for gestational age, birth weight below the 10th percentile for the GA

[¶]Extremely low birth weight infants, birth weight less than 1,000 g

**Caesarean section

Table 2 Risk factors for copper deficiency (multivariate analysis)

Characteristics	Odds ratio	95% CI [†]	P-value
GA [‡] <32 weeks	6.192	1.057-36.264	0.043*
Birth weight<1500 g	0.561	0.095-3.317	0.524
Male	2.175	0.701-6.754	0.179

*p <0.05

[†]CI= confidence interval; [‡]GA=gestational age

ficient group and 92.9±15.8 in the non-deficient group (p<0.001). Accordingly, the percentage of patients who were supplemented with IV copper was significantly higher in the copper-deficient group than in the non-deficient group, with 22 patients (56.4%) and four patients (16.7%) (p=0.002), respectively. PN duration was longer in the copper-deficient group (106.5±97.4 days)

than in the non-deficient group (90.0±61.7 days), but there was no statistically significant difference between the two. The copper-deficient group had a longer NICU stay (p=0.017), lower ANC levels (p=0.027), lower hemoglobin levels (p=0.007), a lower platelet count (p=0.042), and higher proportions of BPD (p=0.003) and rickets (p=0.016) compared to the non-deficient group (Table

Table 3 Clinical and nutritional characteristics

Characteristics	Total patients (n=63)	Cu deficient (n=39)	Cu non-deficient (n=24)	P-value
Serum copper concentration($\mu\text{g/dL}$)	63.0 $\pm$ 27.8	44.6 $\pm$ 14.2	92.9 $\pm$ 15.8	<0.001*
Serum zinc concentration [†] ($\mu\text{g/dL}$)(n=38/24)	87.6 $\pm$ 25.4	85.0 $\pm$ 18.7	91.5 $\pm$ 33.4	0.389
hs-CRP	1.6 $\pm$ 2.7	1.1 $\pm$ 2.0	2.5 $\pm$ 3.5	0.099
IV copper administration, n (%)	26 (41.3)	22 (56.4)	4 (16.7)	0.002*
IV copper (n=22/4)				
Neotrace, n	11	10	1	
Furtman, n	15	12	3	
PN duration, days	100.2 $\pm$ 85.4	106.5 $\pm$ 97.4	90.0 $\pm$ 61.7	0.459
PN calorie [†] (kcal/kg/day)	60.1 $\pm$ 36.8	60.5 $\pm$ 34.0	59.6 $\pm$ 41.8	0.928
EN volume [†] (mL/kg/day)	61.2 $\pm$ 59.8	58.9 $\pm$ 55.5	65.0 $\pm$ 67.2	0.701
EN formula				0.482
NPO, n	22 (34.9)	14 (35.9)	8 (33.3)	
Breast milk, n	12 (19.0)	9 (23.1)	3 (12.5)	
Formula milk, n	29 (46.0)	16 (41.0)	13 (54.2)	
NEC, n (%) ($\geq$ Stage 2)	16 (25.4)	9 (23.1)	7 (29.2)	0.590
GI operation, n (%)	51 (81.0)	32 (82.1)	19 (79.2)	1.000
Stomy, n (%)	37 (58.7)	23 (59.0)	14 (58.3)	0.960
Stomy site (n=23/14)				0.218
Ileostomy, n	31	18	13	
Jejunostomy, n	8	7	1	
Stomy output [†] (mL/kg/day)(n=23/13)	23.6 $\pm$ 16.1	24.3 $\pm$ 17.0	22.4 $\pm$ 14.8	0.747
Cholestasis, n (%)	28 (44.4)	18 (46.2)	10 (41.7)	0.728
T.bil	2.7 $\pm$ 2.4	2.7 $\pm$ 2.3	2.7 $\pm$ 2.5	0.904
RDS, n (%)	38 (60.3)	27 (69.2)	11 (45.8)	0.065
BPD, n (%)	31 (49.2)	25 (64.1)	6 (25.0)	0.003*
PDA treatment, n (%)	31 (49.2)	22 (56.4)	9 (37.5)	0.145
Sepsis, n (%)	36 (57.1)	22 (56.4)	14 (58.3)	0.881
Rickets, n (%)	25 (39.7)	20 (51.3)	5 (20.8)	0.016*
ANC (/ μL)	5285.9 $\pm$ 4508.2	4146.7 $\pm$ 2978.6	7137.2 $\pm$ 5861.0	0.027*
Hemoglobin (g/dL)	9.8 $\pm$ 1.6	9.4 $\pm$ 1.4	10.5 $\pm$ 1.7	0.007*
Platelet (x103/ μL)	262.6 $\pm$ 168.6	225.3 $\pm$ 135.1	323.2 $\pm$ 200.7	0.042*
Total NICU stay, days	96.1 $\pm$ 64.1	111.0 $\pm$ 67.5	71.9 $\pm$ 50.6	0.017*
Total hospital stay, days	149.7 $\pm$ 115.2	158.3 $\pm$ 129.9	135.6 $\pm$ 87.1	0.452

Values are presented as mean $\pm$ SD, or number (%)

*p <0.05; [†]on the day when the serum copper level was measured.

ANC = absolute neutrophil count, BPD = bronchopulmonary dysplasia, EN = enteral nutrition, GI = gastrointestinal, hs-CRP = high sensitivity C-reactive protein, IV = intravenous, NEC = necrotizing enterocolitis, NICU = neonatal intensive care unit, NPO = Nulli (Non) Per Os, PDA = patent ductus arteriosus, PN = parenteral nutrition, RDS = respiratory distress syndrome

Table 4 Subgroup analysis (n=12)

Characteristics	Pre [†]	Post [*]	P-value
Serum copper level (μg/dL)	40.7±14.2	72.1±19.8	0.001*
Preterm (μg/dL) (n=9)	36.9±12.0	67.0±18.5	0.005*
Term (μg/dL) (n=3)	52.0±16.6	87.3±18.0	0.182

Values are presented as mean ± S.D.

*p <0.05

[†] at the day closest to the start of IV copper administration

^{*} at the closest day before the end of IV copper administration

3). Hemoglobin levels of less 10 g/dL were associated with copper deficiency when adjusted for gestational age (OR=3.786; 95% C.I 1.211-11.837; p=0.022).

2. Subgroup analysis

1) Comparison of serum copper concentration before and after IV copper administration

Subgroup analysis was conducted on patients who were administered IV copper and had measured serum copper concentrations before and after copper administration. A total of 12 subjects were analyzed. The average IV copper supplied in the subgroup was 11.6±3.9 μg/kg/day. The average serum copper concentration before IV copper supplementation was 40.7±14.2 μg/dL, and it significantly increased to 72.1±19.8 μg/dL after IV copper supplementation (p=0.001). The average serum copper concentration before copper supplementation tended to be lower in preterm infants than in full-term infants (Table 4). The average postnatal age at the time of serum copper concentration measurement was 123.7±140.4 days before IV copper administration and 186.2±141.6 days after administration. Post serum copper concentrations were

measured at 61.0±42.2 days from the start of IV copper administration.

DISCUSSION

This study found that the incidence of copper deficiency in infants requiring long-term PN was as high as 61.9%. This was similar to a previous study in children receiving PN (with a copper deficiency rate of 50~71%).⁷⁾ However, the previous study included pediatric patients ranging from preterm infants to teenagers. This study focused on infants.

In the group with copper deficiency, gestational age and birth weight were significantly lower and the proportion of preterm infants and extremely low birth weight infants was significantly higher. In particular, gestational age younger than 32 weeks was an independent risk factor for copper deficiency. Since most copper accumulation occurs during the third trimester of pregnancy, copper deficiency can be more likely in preterm infants.⁷⁾

The proportion of BPD patients was significantly higher in the copper deficiency group. Copper is an important component of pulmonary superoxide dismutase, and these antioxidant enzymes can prevent lung injury

caused by oxygenation therapy.^{16),17)} In the copper deficiency group, the proportion of BPD patients may be higher due to the lack of lung injury prevention by antioxidant enzymes.

The copper-deficient group had a longer NICU stay, lower ANC and hemoglobin levels, a lower platelet count, and a higher proportion of rickets. Symptoms of copper deficiency include pancytopenia and skeletal system abnormalities.³⁾ The patients in this study demonstrated such clinical results due to copper deficiency. Therefore, adequate copper supplementation is required to prevent the clinical consequences of copper deficiency.

In baseline characteristics of the subjects of this study, gestational age, birth weight, and the proportion of preterm infants and extremely low birth weight infants was significantly different in both groups. Therefore, further research is needed on the association between copper deficiency and clinical outcomes such as BPD and rickets.

Serum copper concentrations may be increased in patients with acute inflammation and may be falsely elevated when CRP is higher than 4 mg/dL.^{7),18),19)} In this study, hs-CRP tended to be higher in the copper non-deficient group than in the deficient group, but this was not statistically significant. Moreover, the average hs-CRP of all subjects was 1.6 mg/dL, and the average in the copper non-deficient group was 2.5 mg/dL, which was less than 4 mg/dL.

In the subgroup analysis, the average IV copper supply was 11.6 ± 3.9 µg/kg/day. Serum copper concentration increased significantly after IV copper supplementation. The 2005 ASPEN guidelines recommend supplying 20 µg/kg/day of copper to preterm and

term infants and the 2018 ESPEN guidelines recommend 40 µg/kg/day in preterm infants and 20 µg/kg/day (max. 0.5 mg/day) in full-term infants.^{1),14)} In comparison, the copper supply in this subgroup was low. Although IV copper was administered less than the recommended dose, a significant increase in serum concentration was observed. In preterm infants, the average serum copper level after supplementation was 67.0 ± 18.5 µg/dL, which was still within the range of copper deficiency. Especially, more attention is required in premature infants with lower serum copper concentrations. In this subgroup, especially in preterm infants, the copper supply may have been insufficient. A higher copper supply is required based on the ASPEN and ESPEN guidelines.

However, there are several limitations in supplying copper to meet the recommended intake. There is no single-entity IV copper product available in Korea, and the composition of multi-trace element products is often not suitable for infants. Chromium or manganese deficiencies, which are components of multi-trace element products, are rare. These two trace elements can accumulate in patients receiving long-term PN. Manganese accumulation, in particular, raises concerns about neurotoxicity.²⁰⁾ Therefore, single-entity IV copper or multi-trace element products suitable for infants are needed to supply adequate copper to this population.

Since copper is excreted primarily by the liver through the biliary system, it has conventionally been recommended to exclude copper from PN in patients with cholestasis.¹⁰⁾ However, recent studies suggest that this can lead to copper deficiency, and the recommendation is now to supply copper

through PN and monitor serum copper concentrations.¹⁰⁾⁻¹²⁾ In this study, there was no statistically significant difference in the proportion of patients with cholestasis in the copper-deficient and non-deficient groups. The average copper supply in patients with and without cholestasis was 11.8 µg/kg/day and 11.2 µg/kg/day, respectively, which showed no statistically significant difference ($p=0.797$).

This study has the following limitations. First, this study was a retrospective study conducted at a single institution. Several factors, including the timing of copper measurements, were not controlled. The proportions of clinical characteristics may have been underestimated because it was a retrospective analysis based on electronic medical records. Secondly, many subjects were nourished with enteral nutrition and parenteral nutrition, and it was difficult to calculate the amount of copper supplied through enteral nutrition. Among the patients included in this study, 81% had gastrointestinal surgery and 58.7% had gastrointestinal diseases, which made it difficult to estimate the amount of copper supplied through enteral nutrition. Also, there were limitations in quantifying the amount of copper provided through enteral nutrition because the types, methods, and amounts of enteral nutrition varied among the patients. Third, the number of subjects was insufficient, especially in the subgroup, which resulted in reduced statistical power.

It is thought that serum copper concentrations can be reduced due to insufficient body store, depletion during the period when copper is not supplied, and inadequate copper supply. In addition, it is thought that serum copper concentrations may be decreased due

to insufficient absorption of copper due to the immaturity of the gastrointestinal tract, gastrointestinal diseases, and feeding intolerance. Additional studies for optimal copper provision in infants are needed, and individualized dose adjustment is required according to the body store of copper, and the function and absorption rate of the gastrointestinal tract.

This study analyzed the incidence of and risk factors for copper deficiency and evaluated appropriate copper supplementation in infants requiring long-term PN in Korea. The results of this study are a basis in neonatal PN consults to recommend appropriate copper supplementation considering the risk factors of copper deficiency. In the future, a prospective study on the causal relationship between the appropriate copper dosage and clinical outcomes according to gestational age and clinical characteristics in infants on long-term PN is necessary.

CONCLUSIONS

Copper deficiency is common in infants receiving long-term PN without copper, especially in patients with a young gestational age. In the copper-deficient group, ANC, hemoglobin, and platelet counts were lower, and the proportion of BPD and rickets was higher. Therefore, an adequate supply of copper is required to prevent the clinical consequences of a deficiency. It is necessary to develop single-entity IV copper or multi-trace element products with a composition suitable for infants.

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