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Pneumonia-Associated Hypocalcaemia as a Poor Prognostic Factor in the Clinical Outcomes of Infant and Pediatric Intensive Care Unit Patients

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Abstract

Objectives: Pneumonia, as one of the most common and serious diseases in the pediatric intensive care unit (PICU), is associated with electrolyte imbalance. The prognostic value of pneumonia-associated electrolyte imbalance and its effect on the clinical outcome of admitted patients in PICU was considered as the main scope of this study.

Materials and Methods: This prospective observational study was conducted on 8 beds of PICU for two years. In parallel with the routine treatment protocol, the levels of magnesium (Mg), phosphate (P), and calcium (Ca) on the admission day were measured in 240 hospitalized patients with pneumonia. Based on clinical outcomes, patients were categorized into three groups. Finally, the demographic data and electrolyte imbalances were analyzed based on the aim of the study.

Results: There were no significant differences regarding age and gender, as well as the percentages of patients with mechanical ventilation and dopamine administration. In addition, no differences were observed in the lengths of mechanical ventilation and dopamine administration among the three groups. Furthermore, the length of PICU and hospital stays was significantly longer in patients either as discharged with the sequel or dead ones. The results further revealed that the scores of the pediatric risk of mortality and sequential organ failure assessment were significantly higher in patients that passed away. Moreover, Ca and Mg deficiencies were significant in patients either as discharge with the sequel or dead ones. Additionally, 16.2% and 25% of patients who discharged with the sequel and passed away showed P deficiency, respectively. Finally, Ca deficiency by 12.39 times increased patients' poor prognostic clinical outcomes.

Conclusions: Among primary electrolyte deficiencies, hypocalcaemia can be considered as a prominently poor prognostic factor for clinical outcomes in PICU patients with pneumonia but hypomagnesaemia and hypophosphatemia do not predict clinical outcomes.

Keywords: Hypocalcaemia, Pneumonia, Pediatric intensive care units

Introduction

Pneumonia, as a common and serious disease, can lead to death in children who are younger than 5 years old (1,2). The World Health Organization algorithm addressed the pneumonia diagnosis based on simple clinical signs such as tachypnea or respiratory distress in children with coughing or difficult breathing (3). Pneumonia is of different types including community (CAP), hospital (HAP), healthcare-associated (HCAP), and ventilator-associated (VAP) pneumonia (4). CAP is the reason for 15% of the death of children under 5 years old globally (5). Concomitant with pneumonia, other problems such as metabolic and respiratory acidosis, electrolyte disorders encephalopathy, and disseminated intravascular coagulation may occur as well (6). The higher incidence of electrolyte disorders in critically ill patients is a prominent issue that occurs during the course of stay in the intensive care unit (ICU). Hence, the monitoring of electrolytes in ICU patients should be scheduled routinely (7).

Magnesium Mg, calcium (Ca), sodium, and P disorders are common in patients admitted to ICU (8). Although the prevalence of hypernatremia in pneumonia is low (9), hyponatremia has been described as the most common electrolyte abnormality in hospitalized patients (10, 11), which is also related to the severity of pneumonia in children and adults (12). In addition, hypophosphatemia occurs in 28.8%-34% of ICU patients (13). Various reasons can result in hypophosphatemia, including refeeding, malnutrition, diuretic or steroid consumption, catecholamines and antacids, excessive parenteral glucose administration, sepsis, and respiratory alkalosis (14). Further, hypophosphatemia induces respiratory muscle dysfunction (15) by decreasing the availability of phosphate-containing energy sources (16). Furthermore, hypocalcaemia has been introduced as another important problem among patients admitted to the pediatric intensive care unit (PICU). It can induce neuromuscular impairment with cramps, respiratory muscle tetany that

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can be followed by laryngospasm and apnea (17). Moreover, hypomagnesaemia, as another common electrolyte disorder, is frequently ignored in ICU patients (18). It should be noted that this disorder can induce respiratory depression through neuromuscular hyperexcitability (19). In a study by Oduwole et al, no differences were reported between children with and without pneumonia in terms of Ca, P, and Mg levels (20). In another study by El Beleidy et al on 70 critically ill children, 34% Ca, 31% Mg, and 47% P deficiencies were reported in patients with wide ranges of complications (21). In the above-mentioned study, 35.5% of included children suffered from pneumonia, and hypophosphatemia was considered as the most frequent and underestimated electrolyte disturbance. Thus, the present study aimed to evaluate the incidence of Mg, Ca, and P disturbance specifically in children with pneumonia. Eventually, the prognostic value of each electrolyte disturbance and clinical outcomes was specifically considered as well.

Materials and Methods

Study Design

This prospective observational study was conducted in the Pediatric Health Research Center, Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran. Patients were hospitalized at 8 beds of the infant and PICU from January 2018 to January 2020. Only patients with diagnosed pneumonia and within the age range of one month to 13 years old were enrolled in this study. Pneumonia diagnosis was defined as the occurrence of tachypnea with a respiratory rate greater than 60 breaths/minutes in infants younger than 2 months old, greater than 50 breaths/minutes in children of 2 to 12 months old and greater than 40 breaths/minutes in children of 1 year to 5 years old (3). According to the routine treatment protocol of the department, mechanical ventilation and vasopressor were administered to patients as necessary. In the present study, low-dose dopamine was uniformly administered to almost all enrolled patients (22). Dopamine, as an endogenous catecholamine, exerts widespread effects both on neuronal (as a neurotransmitter) and non-neuronal (as an autocrine or paracrine agent) tissues. Additionally, low-dose dopamine plays a prominent role in the regulation of electrolyte balance by increasing renal blood flow (23,24). Demographic data such as age, gender, PICU, and hospital lengths of stay were recorded, and then the severity of patients' illness status was monitored based on the pediatric risk of mortality (PRISM) and sequential organ failure assessment (SOFA)scores according to (25, 26). To measure the plasma levels of Mg, Ca, and P on admission day, parents were asked to fulfill written consent that was approved by the Ethical Committee of Tabriz University of Medical Sciences. Next, patients' clinical outcomes were categorized into discharge with improvement and discharge with sequel and death. Finally, 80 patients were included in each categorization. On the other hand, patients with underlying diseases such as a history of chronic renal disorders, renal replacement therapy, endocrinal disturbance, and chronic diarrhea were excluded from the study.

Statistical Analysis

Continuous and categorical variables were expressed as the mean ± standard error of the *mea*n and percentage (%), respectively. Additionally, chi-square and Fisher exact tests were applied to compare categorical variables. Similarly, the normal distribution of continuous variables resulted in the application of one-way ANOVA with Tukey's post hoc for further analysis. In addition, the association of multiple quantitative and qualitative independent variables with categorized clinical outcomes was assessed by stepwise logistic regression analysis. The statistically significant level was considered as $P < 0.05$, and finally, data were analyzed using SPSS software, version 20.

Results

The contributed patients were categorized based on clinical outcomes including discharge with improvement, along with discharge with the squeal and dead ones. Based on the results, no significant differences were observed regarding the age and gender of categorized patients. Demographic analysis in Table 1 showed that almost all patients needed mechanical ventilation and vasopressor administration (hours). However, the length of mechanical ventilation and vasopressor administration demonstrated no significant differences between the three categorized patients. Conversely, the length of PICU stay (day) in discharged patients with improvement was significantly shorter compared to those who either discharged with the sequel or passed away ones. Similarly, the length of stay in the hospital was significantly shorter in discharged patients with improvement (21.12 ± 6.04 days) in comparison to those who discharged with the sequel (31.41 ± 8.19 days) and passed away ones (33.00 ± 7.48 days). Further, PRISM and SOFA scores were significantly higher in patients who passed away compared with discharged ones.

Based on the age and clinical outcome categorizations, the effects of mean levels of ionized magnesium (Mg), phosphate (P), and calcium (Ca) on the admission days of patients are presented in Tables 2, 3, and 4, respectively. At the lower row of each table, the incidence of patients with deficient electrolytes was reported in each categorized clinical outcome. Regardless of age categorization, Mg and Ca deficiencies were observed in all patients who passed away. Furthermore, the P deficiency in patients who ended up with death was only observed in children aged between 4 and 11 years old (Table 3). Although the average of Mg, P, and Ca showed an increasing trend in discharged patients in comparison with those who passed away, patients who discharged with sequel represented the degrees of Mg and Ca deficiencies in some age categorization (Tables 2 and 4). The percentages of patients with Mg, P, and Ca

Table 1. Demographic, Treatment, and Clinical Data Based on the Categorization of Clinical Outcomes

		Clinical Outcomes		
		Discharge With Improvement (n=80)	Discharge With Sequel (n=80)	Death (n=80)
Age (year)		4.04±3.70[a]	4.10±4.58[a]	3.98±4.93[a]
Gender	Male (%)	56.2% [a] (n=45)	57.5% [a] (n=46)	60% [a] (n=48)
	Female (%)	43.8% [b] (n=35)	41.5% [b] (n=34)	40% [b] (n=32)
Mechanical ventilation (%)		91.2 [a] (n=73)	100 [a] (n=80)	100 [a] (n=80)
Length of mechanical ventilation (h)		190.12±143.33 [a]	238.25±197.56 [a]	270.62±161.06 [a]
Vasopressor (%)		90.0 [a] (n=72)	100 [a] (n=80)	100 [a] (n=80)
Length of vasopressor administration (h)		137.40±102.18 [a]	178.33±128.61 [a]	181.96±87.66 [a]
PICU length of stay (day)		11.68±5.60 [a]	16.33±8.46 [ab]	22.36±8.81 [b]
Hospital length of stay (day)		21.12±6.04 [a]	31.41±8.19 [b]	33.00±7.48 [b]
PRISM score		21.16±10.00 [a]	15.08±7.78 [a]	31.29±4.24 [b]
SOFA score		2.91±1.17 [a]	2.83±.71 [a]	4.00±0.0 [b]

Note. PICU: Pediatric intensive care unit; PRISM: Pediatric risk of mortality; SOFA: Sequential organ failure assessment; Non-similar letters indicate significant differences. $P<0.05$ is defined as the level of significance.

Table 2. The Level of Ionized Magnesium on Admission Day Categorized Based on Age and Clinical Outcomes

Magnesium Level on Admission (mg/dL)	Clinical Outcomes		
	Discharge With Improvement (n=80)	Discharge With Sequel (n=80)	Death (n=80)
7 days- 2 years old (normal range = 1.6-2.6)	1.75±0.02[a]	1.59± 0.13[ab*]	1.32±0.06[b*]
2-14 years old (normal range = 1.5-2.3)	1.80±0.02[a]	1.52±0.11[ab]	1.36±0.07[b*]
Percentages of patients with deficient Ionized magnesium (%)	0 (n=0)	33.7 (n=27)	71.2 (n=57)

Note. * Defined as deficiency. Non-similar letters indicate significant differences. $P<0.05$ is defined as the level of significance.

Table 3. The Level of Phosphate on Admission Day Categorized Based on Age and Clinical Outcomes

Phosphate Level (mg/dL)	Clinical Outcomes		
	Discharge With Improvement (n=80)	Discharge With Sequel (n=80)	Death (n=80)
1-3 years old (normal range = 3.8-6.5)	4.63±0.11[a]	3.97±0.25[b]	3.88±0.12[b]
4-11 years old (normal range = 3.7 -5.6)	4.66±0.07[a]	3.87±0.02[b]	3.55±0.20[*b]
12-15 years old (normal range = 2.9-5.4)	4.9±0.30[a]	4.0±0.06[b]	3.30±0.25[b]
Percentages of patients with deficient phosphate (%)	0 (n=0)	16.2 (n=13)	25 (n=20)

Note. * Defined as deficiency. Non-similar letters indicate significant differences. $P<0.05$ is defined as the level of significance.

Table 4. The Level of Calcium on Admission Day Categorized Based on Age and Clinical Outcomes

Calcium level (mg/dL)	Clinical Outcomes		
	Discharge with improvement (n=80)	Discharge with sequel (n=80)	Death (n=80)
Up to 1 years old (normal range = 1.11-1.44)	1.22±0.02[a]	1.02±0.03[*b]	0.98±0.02[*b]
1-12 years old (normal range = 1.29-1.31)	1.29±0.001[a]	1.10±0.07[*b]	0.96±0.02[*ab]
>12 years old (normal range = 1.05-1.35)	1.22±0.08[a]	1.13±0.02[b]	1.0 ±0.01[*b]
Percentages of patients with deficient calcium (%)	10 (n=8)	75 (n=60)	95 (n=76)

Note. * Defined as deficiency. Non-similar letters indicate significant differences. $P<0.05$ is defined as the level of significance.

deficiencies demonstrated that the incidence of electrolyte deficiencies increased by deteriorating clinical outcomes (Tables 2, 3, and 4). To identify the prognostic value of variables, the association of multiple quantitative and qualitative independent parameters and the effect on the clinical outcomes was analyzed by stepwise logistic regression analysis (Table 5). Accordingly, patients with lower levels of plasma Ca on the admission day faced with deteriorating clinical outcomes.

Discussion

The worldwide prevalence of pneumonia in children was nearly 138 million patients in 2015. Although the prevalence and mortality of pneumonia in children have reduced by 22% and 47%, respectively, during the two recent decades, decreasing the incidence of pneumonia remains one of the major challenges for the World Health Organization (27). Moreover, the monitoring of electrolyte disorders in critically ill patients

Table 5. The Association of Multiple Quantitative and Qualitative Independent Variables With Categorized Clinical Outcomes

	Estimate ± SE	Wald	95% CI	*P* Value
Age	-0.02±0.05	0.19	-0.13–0.08	0.662
Length of mechanical ventilation	-0.003±0.00	3.11	-0.006–0.0	0.07
Length of vasopressor administration	0.003±0.00	0.31	-0.008–0.01	0.57
PICU length of stay	-0.14±0.09	2.32	-0.33–0.02	0.12
Hospital length of stay	0.10±0.09	1.40	-0.07–0.28	0.23
PRISM score	-0.008±0.06	0.01	-0.13–0.11	0.89
SOFA score	-1.58±0.93	2.85	-3.42–0.25	0.09
Ca	21.26±6.04	12.39	9.42–33.10	0.00
P	0.20±1.10	0.03	-1.96–2.37	0.85
Ionized mg	2.67±2.73	0.95	-2.68–8.03	0.32

Note. SE: Standard error; CI: Confidence interval; PICU: Pediatric intensive care unit; PRISM: Pediatric risk of mortality; SOFA: Sequential organ failure assessment; Ca: Calcium; P: Phosphate; Stepwise logistic regression analysis. $P<0.05$ is defined as the level of significance.

is taken into consideration because of its therapeutic values (7,8,21). Although some studies (6,21) reported electrolyte imbalances in PICU patients with various fate of hospitalization, discrepant data were also provided about the lack of electrolyte imbalances in children with and without pneumonia (20). The findings of this study showed that children with pneumonia in the PICU who had also electrolyte imbalances faced deteriorating clinical outcomes. Specifically, hypocalcaemia can be considered as a prominently poor prognostic factor of clinical outcomes in PICU patients.

Mg, as a 'chronic regulator' of biological functions, controversially discussed to represent blood fluctuation by respiratory illness such as asthma (28,29). Although Mg deficiency was primarily measured in PICU patients who ended up with deteriorating clinical outcomes, our data represented no association between the final outcome of PICU hospitalization and Mg deficiency. Similarly, it was reported that the level of Mg had no effect on hospitalization, PRISM score, and the improvement rate of critically ill children (21). The findings of another study on hospitalized children with pneumonia indicated that the Mg deficiency at the admission day was compensated and reached its normal level in discharged patients (30).

Hypophosphatemia, as a common phenomenon in the first ten days of ICU hospitalization, can induce respiratory distress by itself (31). It was reiterated that the slow slope of decreasing the P level until the tenth day of PICU admission has no effect on the PRISM score and the duration of children's hospitalization (21). Our data demonstrated that hypophosphatemia could not be considered as a prominent primary deficiency in different categories of patients. Although the higher incidence of P deficiency was observed in discharged patients with the sequel and passed away ones, no association was found between hypophosphatemia and clinical parameters and outcomes.

Additionally, hypocalcaemia in PICU patients was reported with an incidence between 35 and 44% in India and Iran, respectively (32,33). Ca, as one of the most important ions with various roles in the cells, should be critically balanced in the body. In addition, hypocalcaemia can result in neuromuscular impairments with cramps, respiratory muscle tetany that leads to laryngospasm and apnea (17). Moreover, the altered level of intracellular Ca can induce systemic inflammatory response syndrome by increasing some inflammatory factors such as tumor necrosis factor-alpha, interleukin (IL)-1, IL-2, and IL-6 (34). To the best of our knowledge, some studies concluded that hypocalcaemia increases the mortality and time of hospitalization in critically ill patients (32,33,35). This imbalance in PICU patients increases the risk of vasopressor administration as well (15). Based on the obtained data in the present study, patients with deteriorating outcomes represented a higher incidence of primary Ca deficiency. Contrarily, Oduwole et al showed no difference in the blood level of Ca between pneumonia and control children (20). Eventually, Ca deficiency by 12.39 times increased patients' poor prognostic clinical outcomes. Accordingly, further research is needed to shed light on the therapeutic compensatory borderline in PICU children with pneumonia.

Conclusions

In general, electrolyte balance is assumed as a prominent issue in critically ill patients, especially in the pediatric treatment strategy. Pneumonia, with a high incidence of mortality in children, remains a challenging obstacle in pediatrics. The obtained data indicated that patients with pneumonia in the PICU have a primary electrolyte imbalance. Among primary electrolyte deficiencies, hypocalcaemia can be considered as a remarkably poor prognostic factor of clinical outcomes in PICU patients with pneumonia.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

The Ethical Committee of Tabriz University of Medical

Sciences approved the study (Ethics No. 92121).

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