RESEARCH ARTICLE

Risk Factors for the Development of Critical Illness Polyneuropathy and Myopathy in a Pediatric Intensive Care Unit

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Abstract

Objective

Critical illness polyneuropathy and myopathy (CIPNM) is a major complication of severe critical illness. Previous studies have suggested that many risk factors such as sepsis, multiorgan failure, and neuromuscular blocking agents play a role in CIPNM pathogenesis. The aim of this study was to evaluate possible risk factors in the development of CIPNM in a pediatric intensive care unit (PICU).

Materials & Methods

In this observational study, we recruited 57 patients admitted in the PICU of the Tabriz Pediatric Hospital. CIPNM was diagnosed in 13 (22.8%) patients on the basis of the clinical and electrodiagnostic findings. Different variables such as age, sex, the pediatric risk of mortality (PRISM) score, duration of mechanical ventilation and PICU stay, accompanying pathologic conditions, medications, and in-hospital outcome were compared between the CIPNM and non-CIPNM groups.

Results

Compared to the non-CIPNM patients, the CIPNM patients showed significantly more frequent sepsis (6.8% vs. 38.5%, odds ratio [OR] = 8.5, 95% confidence interval [CI] = 1.7–43.1) and multiorgan dysfunction (43.2% vs. 76.9%, OR = 4.4, 95% CI = 1.1–18.2). Midazolam was administered more frequently in the non-CIPNM group than in the CIPNM group (88.6% vs. 53.8%, OR = 0.2, 95% CI = 0.0–0.6). There was no significant difference between the 2 groups with respect to parameters such as age, sex, PRISM score, duration of mechanical ventilation and PICU stay, other accompanying pathologic conditions, and other medications. The mortality rate was 4.5% in the non-CIPNM group and 15.4% in the CIPNM group.

In the multivariable analysis, sepsis and midazolam administration were the only significant contributors to the development of CIPNM.

Conclusion

Sepsis is an independent risk factor for the development of CIPNM. However, midazolam administration seems to be an independent protective factor against CIPNM.

Keywords: Critical illness polyneuropathy and Myopathy; pediatric intensive care unit; risk factors

Introduction

Neuromuscular weakness delays recovery from critical illness. The 2 types of acquired neuromuscular complications are critical illness myopathy and critical

illness polyneuropathy. However, these 2 terms have some overlaps and instead of that critical illness polyneuropathy and myopathy (CIPNM) is preferred that is a sequela of diffused peripheral neuropathy (1,2). Bolton et al. first described that in 1984 in an adult intensive care unit (ICU) (2). CIPNM has been rarely diagnosed in children, and it is unclear whether the symptoms of CIPNM observed in children differ from those observed in adults (1). CIPNM is mostly asymptomatic, but sometimes it can be symptomatic. About 70% of the patients show electrophysiologic changes associated with axonal polyneuropathy, and 30% of the patients show clinical signs such as flaccid tetraparesis or paraparesis and difficulties in weaning from mechanical ventilation (3,4,5). Two important causes of CIPNM are thought to be sepsis and multiorgan failure (1,2). CIPNM mostly develops in patients who have been ventilator-dependent for at least a week (6). Zifko et al. observed that 70% of the patients with sepsis showed critical illness polyneuropathy (7). Eriksson reported that CIPNM was associated with multiorgan failure caused by sepsis or trauma (8). However, there is an important association between CIPNM and atrophy caused by immobility, acute polyneuropathy, and steroid-induced myopathy. Multiorgan dysfunction, corticosteroid administration, and prolonged immobility are also considered important risk factors; moreover, women are more prone to develop CIPNM than men (9). This study was designed and performed for evaluating peripheral paresis in patients hospitalized in a pediatric ICU (PICU) ward and for identifying risk factors for CIPNM; the patients had no history of known neurologic disorders or events and did not develop them during the hospitalization.

Materials & Methods

We conducted an observational and analytic cross-sectional study and evaluated 57 hospitalized patients admitted to the PICU of the Tabriz Pediatric Educational Therapeutic Center between July 2007 and July 2010. In the 2 years, patients (age range, 1 month to 14 years) who had received mechanical ventilation for at least 1 week were recruited. The incidence of CIPNM and the related factors were evaluated.

Patients with the following conditions were excluded from the study: patients with Guillain–Barre syndrome, acute and chronic spinal lesions, hypophosphatemia, and myasthenia gravis; patients who developed central nervous system disorders and complications during their hospitalization; and patients with confirmed neuromuscular diseases that cause weakness and paralysis.

The patients admitted to the PICU underwent neurologic examinations twice a week. The examinations included evaluation of motor disorders, decrease in muscle mass, loss of sensation, and the status of the tendon reflexes. Patients receiving muscle relaxants and neuromuscular blocking agents were examined 3 days after the cessation of administration of these agents. On the basis of the findings of the clinical and neurologic examinations, electromyography (EMG) and the nerve conduction velocity (NCV) test were performed in patients who were receiving muscle relaxants, had weakness and/or peripheral paralysis, had prolonged weakness and paralysis, and had difficulty in weaning from the ventilator or increase in PCO2 levels after remission of the primary disease. On the basis of the results of the above-mentioned examinations, the patients were categorized into 2 groups: the CIPNM group (if their peripheral weakness was confirmed) and the non-CIPNM group.

The CIPNM patients were followed up after 6 weeks by using neurologic and electrophysiologic analyses.

The time of administration and the dose of medications such as midazolam, pancuronium, steroid, and aminoglycoside were recorded. The levels of creatinine phosphokinase and liver enzymes and the sedimentation rate were examined every 2 weeks. The urine myoglobin level was also measured in this group to check for myopathy.

Muscle biopsies were performed in patients with probable ICU neuromuscular syndrome who were doubted neuromuscular system disorders without known neuromuscular disease. The presence of sepsis and multiorgan dysfunction in the patients was evaluated and recorded by the professors of the PICU ward by using the required diagnostic criteria.

This study was approved by the Ethics Committee of the Tabriz Medical Science University. Written consent was obtained from the parents, and the patients' information

was kept confidential.

Data were analyzed using SPSS16, and the quantitative variables were compared using the Mann–Whitney U test. The qualitative variables were compared using the chi-square test or Fisher's exact test. The independent parameters were determined using the logistic regression test. A p value ≤0.05 was considered statistically significant. The data were presented as mean ± SD, frequency, and percentage values.

Results

Out of the 57 patients, 44 (77.2%) were classified into the non-CIPNM group and 13 (22.8%) were classified into the CIPNM group. The comparison of the demographic data of the 2 groups is summarized in table 1. The percentage of sepsis and multiorgan dysfunction was significantly higher in the CIPNM group than in the non-CIPNM group (table 2). The causes of multiorgan dysfunction in the CIPNM group were sepsis (5 patients), coronary heart disease (CHD; 1 patient), severe pneumonia (1 patient), poisoning (1 patient), tyrosinemia (1 patient), and ischemic–hypoxic encephalopathy (1 patient). The causes of multiorgan failure in the non-CIPNM group were CHD (6 patients), sepsis (3 patients), pneumonia (4 patients), neutropenia (3 patients), medicinal reaction (1 patient), brain hemorrhage (1 patient), and pneumomediastinum (1 patient). The percentage of midazolam administration was significantly higher in the non-CIPNM group than in the CIPNM group (p = 0.01). The CIPNM patients were followed up after 6 weeks. Two patients had died, 8 patients showed complete remission, and 3 patients showed no or slight remission. There were no statistically significant intergroup differences in the other parameters. In the multivariable analysis, there were no significant intergroup differences in the percentage of patients showing multiorgan dysfunction (exp[B] = 4.9; p = 0.08). The percentage of patients receiving midazolam was significantly and independently higher in the non-CIPNM group than in the CIPNM group (exp[B] = 0.1; p = 0.01). The percentage of patients with sepsis was significantly and independently higher in the CIPNM group than in the non-CIPNM group (exp[B] = 7.1; p = 0.04).

Discussion

In the present study, we evaluated the prevalence of and the related factors that cause CIPNM in patients admitted in the PICU of the Tabriz Pediatric Educational Therapeutic Hospital. CIPNM was diagnosed in 22.8% of the patients. The percentage of CIPNM in our study patients was lower than that reported in previous studies. The results of a previous study showed that the prevalence of CIPNM varied from 25% to 77% in PICU patients. This prevalence was reported in the patients who were hospitalized and had received mechanical ventilation in the PICU for at least 7 days (10). Our study patients had also received mechanical ventilation for at least 7 days. Numerous reasons that can explain this difference and the extent of reported area are influential. One of the main objectives of this study was to evaluate the risk factors related to CIPNM. One of the reasons for the difference in the prevalence of CIPNM in the patients of different studies is the heterogeneity of the probable risk factors in these patients. For instance, 70% of the patients with sepsis or systemic inflammatory response syndrome (SIRS) and up to 100% of the patients with multiorgan dysfunction have been shown to develop CIPNM during their hospitalization in the PICU (11,3). However, the diagnosis of CIPNM is difficult in children (12). In most of the CIPNM studies, CIPNM was first diagnosed clinically and electrodiagnostic tests were only performed if required (13). However, only 58% of the children who were clinically diagnosed with CIPNM were confirmed to have the syndrome (10).

In the present study, the diagnosis of CIPNM was confirmed using gold standard tests (electrodiagnostic tests) in all patients. Therefore, all 13 patients diagnosed with CIPNM were confirmed to have the syndrome and the remaining patients were not affected. This is the most important advantage of our study. One of the other probable causes for the difference in the prevalence of CIPNM in the patients of different studies is the lack of a unanimous definition of the status (5). When we evaluated the related causes of CIPNM in the present study, we observed that the percentage of patients with sepsis and multiorgan dysfunction was significantly higher in the CIPNM group than in the non-CIPNM group. However, the administration of midazolam was significantly higher in the non-CIPNM group than in

the CIPNM group. There was no significant difference in the age, sex, duration of hospitalization, immobility, duration of mechanical ventilation, mortality and morbidity rates, and administration of pancuronium, steroid, and aminoglycoside between the 2 groups. In the multivariable analysis, sepsis was found to be an independent risk factor for CIPNM, and midazolam administration was found to an independent protective factor against CIPNM. The results of the previous studies are varied. Hermans et al. concluded that sepsis, multiorgan dysfunction, and SIRS were the major risk factors associated with CIPNM (10). Pati et al. observed that sepsis, SIRS, corticosteroid and aminoglycoside administration, and multiorgan dysfunction were the risk factors associated with CIPNM (14). Shceickert et al. reported immobility as a risk factor for CIPNM (15). In other studies, parameters associated with the development of CIPNM were the duration of mechanical ventilation; duration of hospitalization and PICU stay; aminoglycoside administration; sex (women are more prone to develop CIPNM); severity of the primary disease; and corticosteroid, catecholamine, and vasopressor administration. However, in some studies, aminoglycoside and corticosteroid administration was not related to the development of CIPNM (10). In a study performed by Hermans et al., corticosteroid administration played a protective role against CIPNM (16). Therefore, findings of different studies on CIPNM are highly varied and sometimes paradoxical. Deem et al. concluded that identification of risk factors is very difficult, considering the complicated status of the patients in the PICU (17). De Jonghe et al. reported that the small number of patients in the studies on CIPNM is the greatest limitation in identifying factors related to CIPNM. In addition, the varied selection criteria and definitions can be the reason for the inability to attain a decisive conclusion (18). The small sample size of the CIPNM patients was the main limitation of our study. However, a definitive diagnosis of CIPNM can compensate for this limitation to some extent. Although the relationship between sepsis and CIPNM has been confirmed in different studies, our study reported the protective role of midazolam administration for the first time. The only study that was similar to our study was conducted by de Letter et al. In their study, 98 children were hospitalized in the PICU and 32 developed CIPNM. Their results showed that midazolam administration had no significant relationship with CIPNM (19). In their study, the administered midazolam dose was considered only up to the seventh day of mechanical ventilation. We observed no significant relationship between the midazolam dose and the development of CIPNM. The protective mechanism of midazolam is not clear in this study; however, midazolam may probably have an impact on the improved recovery shown by the patients. Further clinical trials need to be conducted for obtaining decisive results.

In conclusion, the percentage of patients with sepsis and multiorgan dysfunction was significantly higher in the CIPNM group than in the non-CIPNM group. The percentage of pancuronium, steroid, and aminoglycoside administration was not significantly different between the 2 groups. In the multivariable analysis, sepsis was found to be an independent risk factor for CIPNM and midazolam administration was found to be an independent protective factor against CIPNM. The results of our study show that sepsis is an independent risk factor for CIPNM in children hospitalized in a PICU. Therefore, strict and early care of these patients and early treatment can prevent the incidence of CIPNM. Furthermore, midazolam administration had a protective effect against CIPNM. Controlled clinical trials need to be conducted to confirm these results.

Table 1: The demographic data of non-CIPNM and CIPNM patients

Variable		Non-CIPNM	CIPNM	p-value
Age (Months)		18.6 ± 37.3	23.4 ± 37.4	0.23
Sex	**Male**	23 (53.8%)	7 (52.3%)	0.92
	Female	21 (46.2%)	6 (47.7%)	
PRISM score at the time of admission		9.5 ± 5.7	9.0 ± 5.4	0.70
Duration of mechanical ventilation (days)		25.1 ± 17.3	24.5 ± 11.8	0.49
PICU stay (days)		28 ± 18.6	26.5 ± 12.2	0.57

Table 2: The risk factors in non-CIPNM and CIPNM patients

Variable	Non-CIPNM	CIPNM	p-value
Sepsis	3 (6.8%)	5 (38.5%)	0.01
Multiorgan failure	19 (48.2%)	10 (76.9%)	0.03
Prolonged immobility	4 (9.1%)	1 (7.7%)	0.068
Malnutrition	5 (11.4%)	1 (7.7%)	0.58
Midazolam administration	39 (88.6%)	7 (53.8%)	0.01
Duration of midazolam administration (days)	21.1 ± 17.1	27 ± 13.3	0.33
Pancuronium administration	9 (20.5%)	3 (23.1%)	0.56
Duration of pancuronium administration (days)	2.5 ± 0.8	2.0 ± 1.0	0.50
Steroid administration	26 (59.1%)	10 (76.9%)	0.33
Duration of steroid administration (days)	20 ± 19.4	18.2 ± 10.3	0.90
Aminoglycoside administration	17 (38.6%)	7 (53.8%)	0.33
Duration of aminoglycoside administration (days)	12.3 ± 5.2	16.8 ± 3.7	0.06
Prognosis (death)	2 (4.5%)	2 (15.2%)	0.22

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