

ORIGINAL WORK



Intensive Care Unit—Acquired Weakness in Children: A Prospective Observational Study Using Simplified Serial Electrophysiological Testing (PEDCIMP Study)

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Abstract

Background: To study the incidence and time of onset of intensive care unit—acquired weakness in a prospective cohort of children (2–12 years) by serial simplified electrophysiological assessment (Pediatric Critical Illness Myopathy Polyneuropathy study, PEDCIMP).

Methods: A single-center, prospective cohort study (Trial Registry Number: NCT02763709; PEDCIMP2016) was conducted at the pediatric intensive care unit of a tertiary care hospital in North India. A complete electrophysiological evaluation (4 motor nerves and 2 sensory nerves) was performed at baseline in children (2–12 years) admitted to the ICU with a pediatric risk of mortality (PRISM) of > 20 with more than 24-h stay. Following the entry evaluation, a minimal alternate day simplified electrophysiological testing of the unilateral common peroneal nerve and the sural nerve was assessed. A 25% reduction in compound muscle action potential (CMAP) and sensory nerve action potential from baseline was considered significant for ICUAW and was confirmed by complete electrophysiological re-evaluation.

Results: Of the total 481 children assessed for eligibility, 97 were enrolled. The median age of the cohort was 7 years. Sepsis (81%); need for vasoactive support (43%); multiorgan dysfunction (26%) were the common reasons for admission. Of the 433 eligible patient ICU days, 380 electrophysiological observations were done. A significant decrease of > 25% in CMAP of common peroneal nerve was not detected in any of the 380 observations. However, two children unfit for inclusion were diagnosed with ICUAW during the study period.

Conclusions: Children admitted with PRISM > 20 have a very low incidence of intensive care unit—acquired weakness by serial clinical and abbreviated electrophysiological evaluation.

Keywords: Nerve conduction studies, Critical illness neuropathy, Critical illness myopathy, Critical illness myoneuropathy, ICU weakness, Pediatric critical illness myopathy polyneuropathy study

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Introduction

Intensive care unit—acquired weakness (ICUAW) is an increasingly recognized clinical concern in critically ill patients surviving long periods of ventilation. It is independently associated with adverse short- and long-term clinical outcomes. Though, Bolton et al. reported the first case of critical illness polyneuropathy in 1984 [1], possibly, the first description of the disorder dates back to the late eighteenth century when Osler described the “rapid loss of flesh” in patients with protracted sepsis [2]. The pathophysiological mechanisms underlying ICUAW are essentially unknown and are believed to be a combination of structural and functional alterations in muscle and nerve [3]. Sepsis-related dysfunctional microcirculation with myoneuronal hypoxic-ischemic injury; an acquired sodium channelopathy; and mitochondrial impairment with oxidative stress are some of the proposed factors [4, 5]. The reported incidence in adults depends on the specific subpopulation studied and ranges from 70% in the setting of sepsis to 100% in patients with multi-organ dysfunction after seven days of ventilatory support [6, 7]. In undefined patients requiring mechanical ventilation of at least four days, ICUAW was reported in 25–33% by clinical assessment and in 30–50% on electrophysiological assessment [8, 9]. However, the time course of development of neuromuscular dysfunction in critically ill remains uncertain. A multi-center study by Latronico et al. attempted to address this lacuna in a mixed population of medical and surgical critically ill adults and identified ICUAW as early as two days with an overall reported incidence of 30% [10]

Unlike adults, the data on pediatric ICUAW are limited to the description of a little over 40 children worldwide [11]. The largest prospective study till date has estimated an incidence of 1.7% in children which is much lower than in adults [12]. The low incidence may be due to a lack of awareness of this disorder, difficulties in clinical evaluation in children [13]. Many a time, this clinical problem is often identified at the initiation of weaning after discontinuation of sedation [14]. Furthermore, early recognition is hampered by the need for a bedside complete electrophysiological evaluation. This formal electrophysiological assessment is time-consuming (30–45 min) and is often impractical in the pediatric intensive care unit (PICU) setting. A paucity of prospective studies has made ICUAW a poorly characterized entity in children with lack of data on the incidence; natural history; and prognosis.

This study, the PEDCIMP (Pediatric Critical Illness Myopathy Polyneuropathy Study) study, was a prospective study combining serial clinical and electrophysiological assessments antecedent to the onset of weakness in

critically ill children admitted to the pediatric ICU. Our objectives were to determine the incidence and the time of onset of ICUAW in critically ill children

Materials and Methods

This prospective cohort study was conducted between January 2016 and December 2016 in the PICU of a tertiary care research institute from North India. Children (2–12 years) were screened, and those admitted for a period of more than 24 h in the ICU were eligible for the study. The Institutional ethics committee approval was obtained, and the study was registered at the clinicaltrials.gov website (NCT02763709; PEDCIMP2016).

Inclusion and Exclusion Criteria

Children aged 2–12 years with a pediatric risk of mortality (PRISM) score III of >20 and a minimal ICU stay of more than 24 h were eligible for inclusion. Exclusion criteria were: use of drugs causing neuromuscular blockade; previous or current neuromuscular disorder; or a condition predisposing to neuromuscular impairment (e.g.: Type 1 Diabetes Mellitus, Systemic Lupus Erythematosus, Dermatomyositis, Spinal Muscular Atrophy, Guillain-Barre Syndrome, Neuroparalytic snake envenomation, Myositis); lower limb conditions precluding the nerve conduction study or electromyography (gross edema, fractures, amputation, plaster casts, open wounds, infections). Children with abnormal electrophysiological studies at the baseline examination were secondarily excluded. Children found eligible were included after getting informed consent from parents. Baseline clinical and demographic profile was recorded on a proforma.

Clinical Evaluation

A clinical evaluation was performed at the time of recruitment and then daily till discharge from the ICU. The Glasgow Coma Scale and the Sequential Organ System Failure score (SOFA) were assessed. The muscle strength was evaluated by the manual muscle testing method [15]. Three muscle groups in each extremity (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion) were assessed by Medical Research Council (MRC) scoring system, and the cumulative score was taken as the estimate of motor function (range 0–60) [16]. MRC sum score of <48 was used as the clinical cutoff for ICUAW [6]. The severity of multi-organ failure was assessed by maximum SOFA scores and the delta SOFA scores in all children during ICU stay. The total dose and duration of drug therapy, like steroids, muscle relaxants, sedatives, and inotropes, were also noted.

Electrophysiological Evaluation

Twenty-four hours after admission, baseline electrophysiological evaluation by complete nerve conduction study of 4 motor nerves (median, ulnar, tibial, and common peroneal nerve) and two sensory nerves (median and sural nerve) was performed. Compound muscle action potential (CMAP) from motor nerves and sensory nerve action potential (SNAP) from sensory nerves were assessed. Before the electrophysiological tests, heat packs were applied to the skin if its temperature was below 33 °C. Incremental electrical stimulation of the nerves was done to obtain the best SNAP or CMAP amplitudes. All tests were performed with a Nicolet machine (Nicolet Viking IV, Nicolet Biomedical, Inc., Madison, WI, USA).

The median sensory nerve was stimulated on the volar aspect of the wrist, 2–3 cm proximal to the distal crease after placement of ring-recording electrodes around the proximal (–) and distal (+) interphalangeal joints of the second digit; the sural nerve was stimulated 5–10 cm from the active electrode (–) along the dorsal surface of the leg (calf) after placement of surface-recording electrodes above (–) and below (+) the lateral malleolus;

The median CMAP was recorded by stimulating the volar aspect of the wrist, 2–3 cm proximal to the distal crease, and the elbow over the brachial pulse after placement of surface-recording electrodes over the belly (–) and tendon (+) of the abductor pollicis brevis. The ulnar CMAP was recorded by stimulating the medial wrist, adjacent to flexor carpi ulnaris tendon and below the elbow, 3 cm distal to the medial epicondyle after placement of surface-recording electrodes over the belly (–) and tendon (+) of the abductor digiti minimi. The anterior tibial CMAP was recorded by stimulating the medial ankle, slightly proximal and posterior to the medial malleolus, and the posterior fossa in the midposterior knee over the popliteal pulse after placement of surface-recording electrodes over the belly (–) and tendon (+) of the abductor hallucis brevis. The common peroneal CMAP was recorded by stimulating the anterior ankle, slightly lateral to tibialis anterior tendon, and below fibular head after placement of surface recording electrodes over the belly (–) and tendon (+) of the extensor digitorum brevis.

Serial Evaluation

Following the baseline evaluation, a minimum of alternate day simplified electrophysiological tests were performed. The tests included assessment of; conduction velocity and amplitude of the common peroneal nerve; and sural nerve in one leg. To minimize artifacts, the electrode site was marked, and a similar size electrode was used for each patient daily. The CMAP and SNAP amplitude was measured from baseline to negative

peak. A 25% decrease from baseline CMAP and SNAP measured at ICU admission was arbitrarily taken as the minimum consistently detectable reduction. If CMAP or SNAP decreased by more than 25% on two consecutive days, a complete electrophysiological test inclusive of detailed nerve conduction study and electromyography was performed. If the complete electrophysiological test was consistent with ICUAW, complete weekly nerve conduction tests were planned to replace daily tests until ICU discharge.

Data Presentation and Statistical Analysis

The incidence of ICUAW in adults has been reported to be around 30–50% [17]. Given the lack of pediatric data, we assumed an incidence to be one-fifth of the adult value. With an error of 5% and a confidence interval of 90%, a sample size of 97 children was estimated. Descriptive statistics included mean, median, and interquartile range (IQR) for continuous variables and percentages for categorical variables, with comparisons conducted using Wilcoxon rank-sum and Fisher exact tests, respectively.

Results

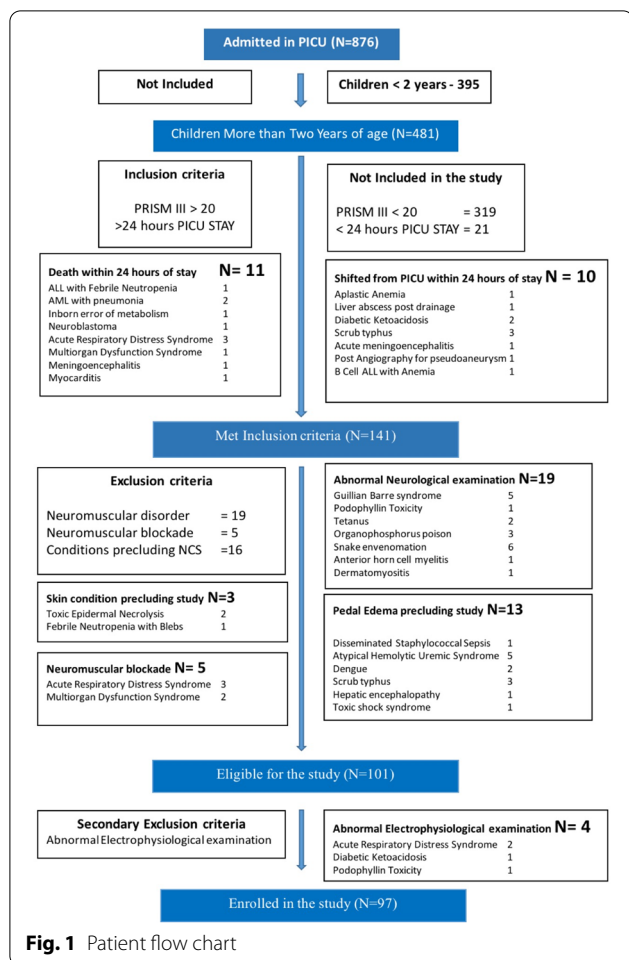
From January to November 2016, a total of 876 children were admitted to the pediatric medical ICU. Among these, there were 101 eligible children for the study (Fig. 1). Ninety-seven children were recruited over one year based on the inclusion and exclusion criteria.

Clinical Profile

The median PRISM III of the cohort was 23 with a median duration of ICU stay was 4 days. Among 56 children who required mechanical ventilation, the median duration of ventilation was 4.5 days, with one child needing 19 days of ventilation. During the PICU stay, sepsis (81%); the need for vasoactive support (43%); hypoalbuminemia (29%) were noted in the majority of the children (Table 1, Supplementary Table 1). The median maximum SOFA score and delta SOFA score were 7 and 2, respectively. Muscle strength evaluation by manual muscle testing was possible only in 22 children at entry examination, and serial examination by MRC grading did not reveal clinical evidence of ICUAW during the PICU stay (Supplemental Table 2). At discharge from PICU, 52 children underwent manual muscle testing, and the MRC sum score was higher than forty-eight in all the tested children.

Electrophysiological Profile

During the study period, of the 101 children enrolled, four children were secondarily excluded following an abnormal baseline electrophysiological examination (Fig. 2). The median duration of screening per patient



was three days, with the longest observation of 20 days. The baseline electrophysiological measurements at entry examination were stratified into three groups based on age (2–4; 5–7; 8–12 years) and were comparable with the available normative data [18] (Table 2). Non-physiological technical factors influenced the assessment of the sural nerve and hence were not analyzed in the study. Eighteen children had an ICU stay of fewer than 48 h with a single electrophysiological recording and hence were excluded from the analysis. In the remaining 79 children, the change in common peroneal nerve CMAP from the baseline to ICU discharge was also stratified, based on the age, into three groups (Table 3). A total of 380 electrophysiological observations were done in the 433 eligible ICU patient days. However, the designated reduction of 25% from the initial value was not detected in any of the 79 serially evaluated children. In a subgroup of children [age 5–7 years ($N=21$)], a statistically significant absolute reduction in the mean CMAPs from the baseline was observed ($P=0.007$) (Table 3). However, the cumulative percentage reduction in the mean CMAPs

Table 1 Characteristics of the 97 children enrolled in the study

Demographic characteristics	All patients ($n=97$)
Male, n (%)	65 (67%)
Age (years)	7 (4–10)
<i>Clinical characteristics</i>	
PRISM III at admission	23 (21–27)
Duration of ICU stay (days)	4 (2–7)
<i>Critical illness characteristics</i>	
Duration of ventilator stay (days) $n=56$	4.5(2–6.75)
Maximum Sequential Organ Failure Assessment score	7 (5–12)
Delta Sequential Organ Failure Assessment score	2 (1–5)
<i>Risk factors^a, n (%)</i>	
Sepsis	79 (81%)
Vasoactive support	42 (43%)
Hypoalbuminemia	28 (29%)
Dysglycemia	15 (15.5%)
Acute kidney injury	14 (14.5%)
Acute respiratory distress syndrome	14 (14.4%)
Health care-associated infection	12 (12%)
Multiorgan dysfunction syndrome	12 (12%)
Renal replacement therapy	10 (10%)
Steroids	09 (9%)
Tracheostomy	04 (4%)
1 risk factor	27 (28%)
2 risk factors	24 (25%)
3 risk factors	14 (14%)
> 3 risk factors	23 (23%)

Data are presented as median (interquartile range), unless stated otherwise

^a Risk factors tabulated here are the predefined risk factors for intensive care unit—acquired weakness in the literature

was found to be 5.7 percent, which was well below the designated 25% cutoff for a more detailed evaluation with no clinical relevance.

Of the 97 children enrolled in the study, eighteen children died, and in five, the parents decided to withdraw life support. The incidence of pediatric ICUAW in children aged 2–12 years admitted for more than 24 h in the ICU setting with a PRISM III of 20 is null, indicating that the incidence in these group of children is likely to be lower than 4.7 percent (95% CI 0–4.75). However, one girl who had an ICU stay of 29 days with a primary diagnosis of scrub typhus deserves special mention. Her 24-h PRISM score was 44 and she had multiple risk factors for ICUAW, including acute respiratory distress syndrome, prolonged ventilation, tracheostomy, vasoactive support, and acute kidney injury. She developed clinically evident proximal weakness in lower limbs on day 19 of hospital stay. In contrast, the serial common peroneal nerve CMAP did not reveal any reduction in amplitudes from

Table 2 Observed mean compound muscle action potential (CMAP) of tested motor nerves in the enrolled children

Age group	2–4 years N = 26	5–7 years N = 25	8–14 years N = 46
	Distal	Distal	Distal
<i>Tibial nerve</i>			
Mean	8.41	9.7	11.3
Standard deviation SD	1.38	1.72	3
-2SD	5.65	6.26	5.3
<i>Common peroneal nerve</i>			
Mean	2.67	2.66	2.78
Standard deviation SD	0.79	0.73	0.79
-2SD	1.09	1.2	1.2
<i>Median nerve</i>			
Mean	3.4	4.5	4.5
Standard deviation SD	1.2	1.56	1.1
-2SD	1	1.38	2.3
<i>Ulnar nerve</i>			
Mean	4.08	4.72	5.06
Standard deviation SD	0.56	0.6	0.6
-2SD	2.96	3.52	3.86

Lower limit of normality (-2SD) is two standard deviations below the normal mean value. CMAP = compound muscle action potential. No measurement was below the < 2 SD of the reference value

the baseline. Nevertheless, by day 26 of ICU stay, the weakness recovered, and the child had good spontaneous antigravity movements in lower limbs. Electromyography, done on day 31 of hospital stay, was unremarkable.

Additionally, during the 12-month study period, two children with super refractory status epilepticus were complicated by ICUAW. Their diagnoses were confirmed by reduced amplitude in all the tested motor nerves suggestive of critical illness polyneuropathy of axonal type. The risk factors identified were the need for vasoactive support, lidocaine infusion, prolonged ventilation, and tracheostomy. These two children were, however, not included in our study as the PRISM III at admission was 15 and 18, respectively. They had persistent clinical and electrophysiological signs of critical illness polyneuropathy at follow-up of six months post-discharge.

During the one-year study period, out of 876 children admitted to the ICU, three developed ICUAW (incidence of 0.34%; CI 0.01–0.1) of whom two had critical illness polyneuropathy (incidence of 0.2%; CI 0–0.8). These children were not a part of the current study as they did not meet the inclusion criteria.

Discussion

This prospective study combining serial clinical and electrophysiological assessments was conducted to

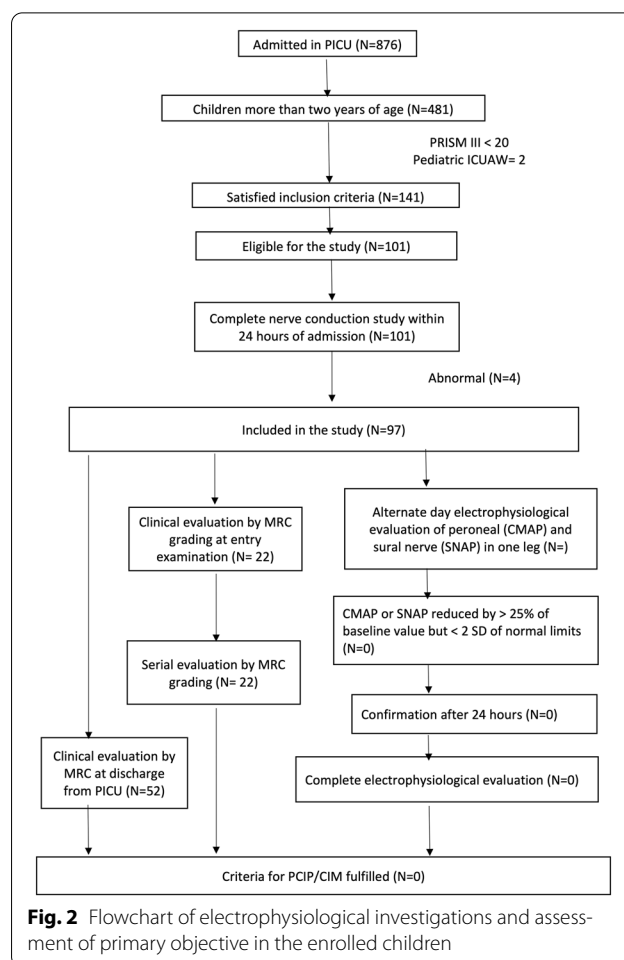


Fig. 2 Flowchart of electrophysiological investigations and assessment of primary objective in the enrolled children

determine the incidence and time of onset of Intensive care unit—acquired weakness in children. The patient characteristics and reasons for admission of our study population are similar to the available literature on ICUAW in children [11, 19]. However, after performing 380 simplified, serial electrophysiological evaluations over one year, we were not able to identify any child with Intensive care unit—acquired weakness. Our observations are in keeping with the results of two of the largest studies involving children. In the study by Banwell et al., among 830 children, the incidence of critical illness polyneuropathy was found to be 1.69% (95% CI 1–6.7%), while a 0.02% incidence was reported by Field Ridley et al. [12, 20].

The diagnosis of Intensive care unit—acquired weakness is strictly clinical and is usually assessed by manual muscle testing or hand-held dynamometry in adults. The MRC scoring is a reliable method of screening for muscle weakness and is typically supported by electrophysiological studies such as nerve conduction study or needle electromyography. In contrast to adults, MRC scoring

Table 3 Change in common peroneal nerve CMAP during ICU stay among different age groups in the enrolled children

Tested Nerve	Age group 2–4 years (Baseline)–(last observation)	Age group 2–4 years (Baseline)–(last observation)
<i>Common peroneal nerve</i>	Absolute change in CMAP	Percentage change in CMAP
<i>N = 20 (Baseline CMAP = 2.67)</i>		
Mean	– 0.07	– 2.6
SD	0.33	14.8
Median	0.01	0.48
<i>P</i> value	0.35	Not significant
<i>Common peroneal nerve</i>	Age group 5–7 years	Age group 5–7 years
<i>N = 21 (Baseline CMAP = 2.66)</i>	Absolute change in CMAP	Percentage change in CMAP
Mean	– 0.15	– 5.2
SD	0.23	9.75
Median	– 0.15	– 5.7
<i>P</i> value	0.007	Significant
<i>Common peroneal nerve</i>	Age group 8–12 years	Age group 8–12 years
<i>N = 38 (Baseline CMAP = 2.78)</i>	Absolute change in CMAP	Percentage change in CMAP
Mean	0.0224	2.0158
SD	0.51	18
Median	0.06	2.41
<i>P</i> value	0.7	Not significant

CMAP *Compound muscle action potential*

is not validated in children, and the clinical diagnosis of ICUAW is challenged by factors such as temperament, psychomotor, and perceptual-motor abilities, and developmental age of the child. The feasibility of MRC scoring in critically ill children was evaluated by Siu et al. and was achieved only in 27% of their cohort during the PICU stay [21]. This is comparable with our data, where MRC scoring was feasible in only 22% of the study population at entry evaluation. This difficulty in assessment is partly addressed by the use of electrophysiological studies in sick children.

In this regard, our longitudinal assessment of unilateral common peroneal nerve performed every other day in sick children may be regarded as a useful bedside screening tool for the early diagnosis of ICUAW. The practical utility of this approach has been well established by the Critical illness myopathy and/or neuropathy (CRIMYNE) study in critically ill adults and has aided in the prompt recognition of ICUAW as early as 2 days [10]. We followed a protocol similar to the multi-centric CRIMYNE study, where a 25% reduction in CMAP of the common peroneal nerve exhibited 100% sensitivity and 67% specificity for ICUAW detection. The relevance of common peroneal nerve as a screening tool was further validated by the CRIMYNE-2 diagnostic accuracy study with 100% sensitivity and a higher 85% specificity [22]. Besides, the common peroneal nerve is an ideal candidate for the

“bio-energetic failure” mechanism of ICUAW, especially during the early stages, where functional (electrical) impairment heralds structural or histological changes in the nerve [23]. The peroneal nerve is the longest nerve in the lower limb and is vulnerable to such low energy hypercatabolic states of tissue ischemia, and this may explain the higher sensitivity in electrophysiological testings. Although not proven in children, we attempted the simplified serial common peroneal testing as a practical alternative to the clinical methods to detect ICUAW.

To the best of our knowledge, this is possibly the largest data prospectively collected in children in the ICU to identify the time of onset and incidence of ICUAW. The children enrolled in the study had diverse, primarily medical conditions, mimicking the patient profile of PICUs worldwide. Systematic electrophysiological evaluation throughout the PICU stay irrespective of the child's cooperation for clinical assessment in an effort to identify ICUAW at the earliest is another strength of the study. Khan et al., using complete nerve conduction studies within 72 h of admission, explored the time of onset of ICUAW in adults with severe sepsis. Early electrical evidence of neuropathy upon enrolment was noted in 63% of the adults and highly correlated with death [24]. The results, however, were confounded by high prevalence of advanced age, diabetes, HIV, alcohol use, and worsening illness scores. On the other hand, the results

from our study have to be analyzed, keeping in mind the relatively few days of PICU stay or mechanical ventilation in our cohort. Besides, the use of PRISM III in our study had some concerns. Children with chronic organ disease and child admitted for post-surgical monitoring had a fallaciously higher PRISM score, possibly diluting the sampled population. Absence of a validated severity risk assessment score at admission for children, unlike the Acute Physiology And Chronic Health Evaluation (APACHE) and Simplified Acute Physiology Score II (SAPS) score in adults, may have played a role in the exclusion of two children with critical illness polyneuropathy from our study group. The two children had persistent clinical and electrophysiological signs of critical illness polyneuropathy at six months post-discharge follow-up. Furthermore, neuromuscular blockade is a documented risk factor for ICUAW, and children on neuromuscular blockade were excluded from the study as one of our objectives was to identify the time of onset of ICUAW.

Based on the available literature on ICUAW in children, the precise reasons for a low incidence in children are still unclear, but we believe there are multiple mechanisms. Axonal transport is a key process of neuronal functionality in peripheral nerves. Children have smaller axonal length and possibly better axonal transport, making their nerves less susceptible to injury. They possibly have a better mitochondrial function, a better restorative neurotrophic factor concentration, and function, protecting nerves and muscles from injury. It has been observed that they have better recovery following immune-mediated peripheral neuropathies [25] and are less susceptible to chemotherapy-induced peripheral therapy [26]. Furthermore, children are further helped by fewer comorbid nerve or muscle-damaging medical conditions like diabetes, cancer, chronic organ failure, or chronic drug use.

Our a priori sample size was estimated at an incidence of 10% based on existing CRIMYNE study (30.4%, 95% CI 21.9–40.4%); we, however, did not factor in the days of mechanical ventilation or duration of intensive stay. As our data suggest that the incidence of critical illness polyneuropathy and myopathy is likely to be lower than 4.7%, for this low incidence and with a 95% confidence interval and one percent margin of error, we would have needed 1585 children. Hence, our study was underpowered to detect the low prevalence of ICUAW in children. Given the paucity of literature on ICUAW in children, future research should include a larger sample size and use simplified electrophysiological evaluation as a screening tool. An alternative approach could be prospective studies with lesser sample size focusing on specific high-risk groups with more than 7-day ventilation such

as multiorgan failure, severe sepsis, patients on high-frequency oscillatory ventilation, ARDS, or polytrauma.

Conclusions

In conclusion, through longitudinal assessment using clinical and abbreviated electrophysiological evaluation, we found that in children admitted to the ICU with a PRISM score > 20, the incidence of intensive care unit—acquired weakness is very low.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s12028-020-01123-x>) contains supplementary material, which is available to authorized users.

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Author contributions

NS conceptualized the study. AK, NS, PS, and MJ prepared the study protocol. AK and IKS collected the data. NS, MJ, PS and JKS supervised the conduct and operational aspects of the work. AK, IKS, NS did the analyses and drafted the manuscript. All authors contributed to the final draft of the manuscript. NS will act as the guarantor.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical Approval

The study was approved by the Institute Ethics Committee.

Informed Consent

Informed consent was obtained from parents/primary caregivers of the enrolled children.

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