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ORIGINAL ARTICLE

Evaluation of ventilatory muscles in infants with severe botulism

Evaluación de la musculatura ventilatoria en lactantes con botulismo grave

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What do we know about the subject matter of this study?

Identifying the best time for extubation in infants with neuromuscular weakness requiring ventilatory support is a challenge. There is limited knowledge regarding the development of diaphragmatic contractile function, as no studies have been conducted in infants suffering from severe botulism.

What does this study contribute to what is already known?

We analyzed the usefulness of ultrasound diaphragmatic excursion and maximal inspiratory and expiratory pressure as parameters of respiratory muscle strength recovery. These parameters increased significantly in all infants with severe botulism during mechanical ventilation. They could be useful tools to identify the best time for extubation in this population and avoid complications.

Abstract

Infant botulism is a toxic infection that causes flaccid muscle paralysis, requiring invasive mechanical ventilation (IMV) in severe cases. Weaning from ventilatory support in this group of patients is challenging due to the difficulties in evaluating the recovery of muscle strength. **Objective:** To evaluate the recovery of ventilatory muscle strength in infants with severe botulism. **Patients and Method:** Demographic variables and daily measurements of maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and diaphragmatic excursion (DE) were retrospectively evaluated in infants with severe botulism who required IMV, from the beginning of ventilatory support (baseline) until extubation (final). **Results:** 10 patients were included with a median age of 4 months (IQR 3.2-4.7); all received equine botulinum antitoxin with a median delay of 89.5 hours (IQR 61.4-114.2). The infants remained in PICU for a median of 15 days (IQR 12.5-16), with requirement of IMV for 15.2 ± 6.4 days. The baseline values recorded of IMV increased progressively, with significant differences compared to the final values (right DE 0.62 ± 0.1 vs 1.09 ± 0.29 cm, MEP 16 ± 6.7 vs 43±17.1 cmH20, and MIP 24 ± 12.4 vs 46 ± 6.9 cmH20, respectively). No patient failed extubation. **Conclusions:** The parameters evaluated significantly improved during botulinum diaphragmatic paralysis. They could be useful tools for mechanical ventilation weaning in children with this neuromuscular weakness.

Keywords:
Infant Botulism;
Diaphragmatic Excursion;
Mechanical Ventilation;
MIP;
MEP

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Introduction

Infant botulism is a life-threatening neuroparalytic toxin-mediated infection in children under 1 year of age, usually residents of peri-urban areas. Although it is the most common form of human botulism, it is a rare disease worldwide. The United States reports the highest number of cases, between 80-100 per year, with California being the state with the highest incidence (6.5 cases per 100,000 live births)[1]. In Argentina, between 50-60 cases are reported annually, with 93 cases having been confirmed between 2017 and 2019, with an incidence of 5.9 cases per 100,000 live births in the latter year[2,3].

The main reservoir of *Clostridium botulinum* is soil. Infants become ill by inhaling and/or swallowing its spores from multiple sources, ranging from items contaminated with environmental dust or soil, to foods such as honey and some medicinal herbs. However, there are cases where the source has not been established[4]. Subsequently, the bacteria colonize the intestinal epithelium, producing toxin, which enters the bloodstream and reaches all the cells of the organism. Botulinum toxin blocks the release of acetylcholine in the presynaptic terminals of the neuromuscular junction and the autonomic nervous system, producing flaccid, symmetrical, descending muscle paralysis, which may progress to death due to respiratory failure. Infants initially present with generalized hypotonia, decreased or absent deep tendon reflexes, and cranial nerve abnormalities such as reduced sucking, swallowing, and coughing reflexes. They may also present autonomic dysfunction, including urinary retention, tachycardia-bradycardia, and hypo- or hypertension. When the patient requires mechanical ventilation (MV) due to significant respiratory muscle involvement, it is considered severe infant botulism, which is highly lethal without treatment[5].

There are human and equine serum botulinum antitoxins, which significantly accelerate the recovery from the disease. However, they do not prevent the development of paralysis, so the main treatment is symptomatic through ventilatory, hemodynamic, and nutritional support and cardiovascular monitoring until the toxin effect ceases[6].

The severity and progression of neuromuscular weakness caused by botulinum toxin are unpredictable, posing practical difficulties for the successful withdrawal of ventilatory support. Fluoroscopy can be used to assess diaphragmatic motion; however, it requires patient transport, exposes the patient to a significant radiation dose, and does not provide information about muscle strength[7]. The latter can be determined by measuring the transdiaphragmatic negative pressure, although this method is expensive and requires trained personnel[8]. In populations with neuromuscular weakness, other predictors of successful extubation have been studied to objectively evaluate respiratory muscle strength and cough capacity[9]. Among them are measurements of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) against an occluded airway. These are non-invasive, quick, and easy bedside assessments, useful to complement the spontaneous breathing trial (SBT)[10]. Specifically, MEP reflects expiratory force, is closely related to lung volume, and is more sensitive than MIP in detecting progression of weakness in children with neuromuscular diseases[11]. It is also related to pulmonary vital capacity, which can predict susceptibility to respiratory infections, need for ventilatory support, and survival in this population[12].

Besides, diaphragmatic ultrasound has also been used to assess contractility and respiratory muscle strength. Specifically, diaphragmatic excursion (DE) is associated with successful extubation in children with 85% sensitivity and 71% specificity[13], although there are no studies that analyze it in infants with severe botulism.

Assessing diaphragmatic contractile function in children on MV is a valuable tool to prevent complications associated with extubation failure, such as prolonged MV, longer hospital stays, and mortality[14]. The objective of this work was to evaluate DE, MIP, and MEP as parameters of respiratory muscle strength recovery in patients with severe infant botulism.

Patients and Method

We retrospectively reviewed medical records of patients admitted to the pediatric intensive care unit (PICU) of the *Hospital Humberto Notti*, a highly complex regional referral center located in the province of Mendoza, Argentina. Children diagnosed with severe infant botulism, who were admitted between March 01, 2017, and February 28, 2018, to the PICU and who required MV were included. Patients with incomplete data in the clinical history, known previous neuromuscular pathology, or hospitalization less than 24 hours were excluded. Patient demographic and descriptive data were collected in a multivariable form. The following was recorded: age, sex, hospitalization time in PICU, invasive MV (IMV) or noninvasive MV (NIV), time from admission to botulinum antitoxin administration, complications, and mortality. Following the study center protocol, infants did not routinely receive sedation and analgesia and underwent SBT daily, with daily recording of DE, MIP, and MEP measurements during their requirement for IMV, as part of routine ventilatory monitoring (from 8 am to 10 am). Baseline measurement was defined as the first measurement performed after intubation, and final measurement as the one performed while SBT before extubation. The latter was decided by the physician in charge according to clinical criteria. The infant was extubated after maintaining spontaneous breathing with 10 cmH_20 of pressure support and 5 cmH_20 of end-expiratory pressure for 30 to 120 minutes, while preserving adequate minute ventilation, respiratory mechanics, heart rate, and oxygen saturation > 92%. If the patient failed SBT, they remained on IMV in assist-control mode, while if they presented clinical respiratory deterioration after extubation, NIV was initiated. Extubation failure was defined as the need for reintubation and IMV within 48 hours of extubation.

MIP and MEP

During the first minutes of daily SBT, the patient was positioned with the head of the bed at 30º, disconnected from the ventilator (0 cmH_2O positive pressure), and an analog manometer with a one-way valve (Rocimex SRL, Argentina) was connected to the endotracheal tube. The airway was occluded during inspiration (MIP) or expiration (MEP) for 25 seconds, followed by a one-minute rest, repeated three times (six measurements in total). The most negative inspiratory value near residual volume (MIP) and the highest positive expiratory value near functional residual capacity (MEP) were recorded[15]. Measurements were performed daily by two trained physiotherapists, randomly, while monitoring clinical hemodynamic and oxygenation parameters during the test. Patients tolerated the expected occlusion time during all measurements without bradycardia or desaturation. Chest physiotherapy and endotracheal secretions suctioning were performed before measurements; however, endotracheal tube leak and equipment dead space were not documented.

Diaphragmatic excursion (DE)

During daily SBT (randomly performed before or after MIP and MEP measurement), a portable Samsung MySono U6 ultrasound machine with a sector transducer (frequencies 3.5 to 5 MHz) was used for diaphragmatic assessments. The probe was positioned in both hypochondria in a cephalocaudal orientation along the right anterior and the left posterior axillary lines. There, the vertical distance between the baseline and the peak of the inspiratory curve in M-mode was measured at the point of greatest diaphragmatic motion, recording the average of three measurements[16]. Measurements were performed daily by four trained physicians, in random order, while monitoring clinical hemodynamic and oxygenation parameters. No patient showed intolerance to the procedure.

Statistical analysis

The systematization and descriptive analysis of the information were performed with Infostat software. Each variable was tested for normality using the Shapiro-Wilk test for small samples, expressing continuous variables with nonparametric distribution as median and interquartile range (IQR); and variables with normal distribution as mean and standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Subsequently, the Student's t-test was performed with paired data for variables with normal distribution. A p-value < 0.05 was considered statistically significant.

Ethical considerations

The conduct of this study did not affect the type or quality of care provided, and there were no risks inherent to participation. The project was approved by the Health Research Ethics Committee of the *Hospital Humberto Notti* on May 24, 2023 (Act Nº 59/2023). Patient data confidentiality was ensured and used only for this study.

Results

In the observed period, 16 patients with infant botulism were detected in Mendoza, and 13 of them were admitted to the *Hospital Humberto Notti*. Among them, 10 presented severe infant botulism with respiratory failure, were admitted to the PICU for ventilatory support, and were included in this study. 80% were male (n = 8), with a median age of 4 months (IQR 3.2-4.7) and normal weight for their age. In all cases, confirmatory diagnosis was performed by mouse bioassay (*Universidad Nacional de Cuyo*), identifying *Clostridium botulinum* toxin A. Immediately after botulism was confirmed, all infants received equine botulinum antitoxin with a median delay of 89.5 hours (IQR 64.1-114.2) from symptom onset to administration. Their PICU stay had a median of 15 days (IQR 15.5-16), with a median of IMV requirements of 15.2 days (±6.4). After extubation, 50% of them required NIV for 0 to 4 days due to respiratory distress. Complications were observed in 40% of the patients during their PICU stay, although none of them were reintubated or died. table 1 shows descriptive data.

Diaphragmatic excursion

Daily measurements of both hemidiaphragms increased in each infant as the disease progressed, with significant differences between the mean baseline and final right DE of the 10 patients (mean 0.62 ± 0.1 vs. 1.09 ± 0.29; $p < 0.05$) (table 2, figure 1). In addition, patients with longer days of IMV had higher final right DE values (table 2).

Table 1. Patient demographic data

Patient	Age (months)	Sex	Weight (kg)	Hospitalization time (days)	Hospitalization time in PICU (days)	IMV (days)	NIV (days)	Time from admission to botulinum antitoxin administration (hours)	Complications
1	3	F	5.2	47	12	10	2	63	No
2	1	M	4.6	41	22	23	1	67	ASP
3	4	M	7.1	28	8	8	1	95	No
4	5	M	8.3	31	10	10	0	120	ASP
5	5	M	9.4	33	15	15	0	97	Atelectasis
6	5	M	8.1	40	16	12	4	84	No
7	4	F	7.9	29	15	15	0	60	No
8	4	M	8.0	52	14	14	0	57	No
9	1	M	5.2	34	16	16	0	310	No
10	4	M	7.7	59	40	29	1	144	VAP
Shapiro-Wilk (p)	0.01#	-	0.173	0.328	0.004#	0.125	0.003#	< 0.001#	-
Median (IQR)	4 (3.2-4.7)	-	-	-	15 (12.5-16.0)	-	0.5 (0-1)	89.5 (64.1-114.2)	-
Mean (Standard deviation)	-	-	7.1 (1.6)	39.4 (10.4)	-	15.2 (6.4)	-	-	-

Quantitative variables with a normal distribution (Shapiro-Wilk p > 0.05) are presented as mean values, while those with a non-parametric distribution (Shapiro-Wilk p < 0.05) are presented as medians. Sex: F = female, M = male. PICU: Pediatric Intensive Care Unit. IMV: Invasive Mechanical Ventilation. NIV: Noninvasive Ventilation. ASP: Aspiration Pneumonia. VAP: Ventilator-Associated Pneumonia. IQR: Interquartile Range. # Non-parametric distribution.

Table 2. Individual measurements of DE, MEP and MIP

Patient	Left DE (cm)		Right DE (cm)		MEP (cmH20)		MIP (cmH20)	
	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final
1	0.76	1.00	0.68	0.82	30	52	-40	-32
2	0.91	1.41	0.64	1.44	8	40	-24	-46
3	0.80	0.88	0.74	0.80	16	38	-32	-48
4	0.82	0.76	0.38	1.09	20	48	-24	-52
5	1.00	0.91	0.56	1.02	20	84	-26	-58
6	0.46	1.03	0.69	1.03	20	44	-20	-48
7	0.61	0.90	0.69	0.95	8	24	-8	-40
8	0.58	0.89	0.60	1.17	12	48	-11	-44
9	0.54	0.89	0.63	0.85	11	28	-12	-44
10	0.53	1.87	0.59	1.73	15	28	-21	-48
Mean	0.70	1.05	0.62	1.09	16	43	-24	-46
Standard deviation	0.18	0.34	0.10	0.29	6.78	17.18	12.44	6.93
Shapiro-Wilk (p)	0.54	0.002#	0.10	0.10	0.36	0.09	0.78	0.71
Paired Student's t-test (p)	-		0.0017*		0.0002*		0.0012*	

The first rows list the individual data of the 10 included patients (each value represents the average of 3 measurements). Infants who experienced complications (patients 2, 4, 5, and 10) showed higher values of diaphragmatic excursion (DE) and maximum inspiratory pressure (MIP) on the day of extubation (final). Female infants (patients 1 and 7) had lower MIP values compared to males on the day of extubation (final). Patients who required invasive mechanical ventilation (IMV) for more than 21 days (patients 2 and 10) presented higher DE values at the time of ventilatory support withdrawal (final). IMV: Invasive Mechanical Ventilation. DE: Diaphragmatic Excursion. MIP: Maximum Inspiratory Pressure. MEP: Maximum Expiratory Pressure. Baseline: Day of IMV initiation. Final: Last day of IMV. #Non-parametric distribution. *Statistically significant.

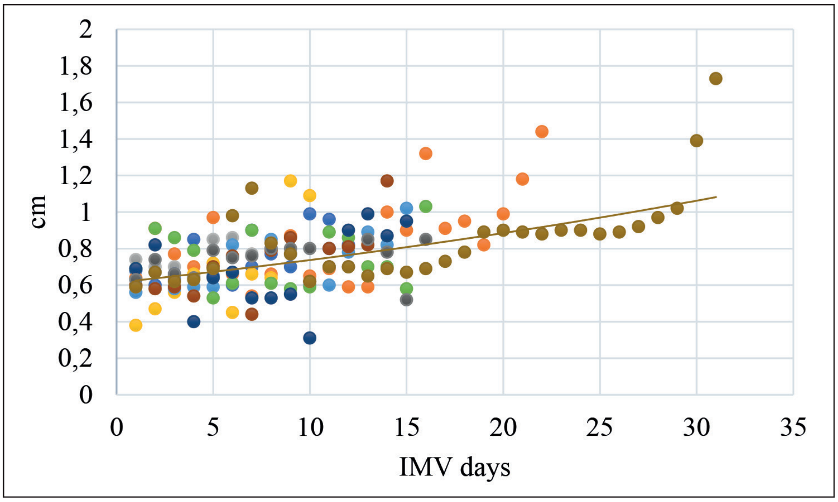

Figure 1. Right diaphragmatic excursion. Individual daily values of right diaphragmatic excursion measured by ultrasound during invasive mechanical ventilation. Each patient is represented by a different color. Daily values represent the average of three measurements per infant (N = 10). IMV: Invasive Mechanical Ventilation.

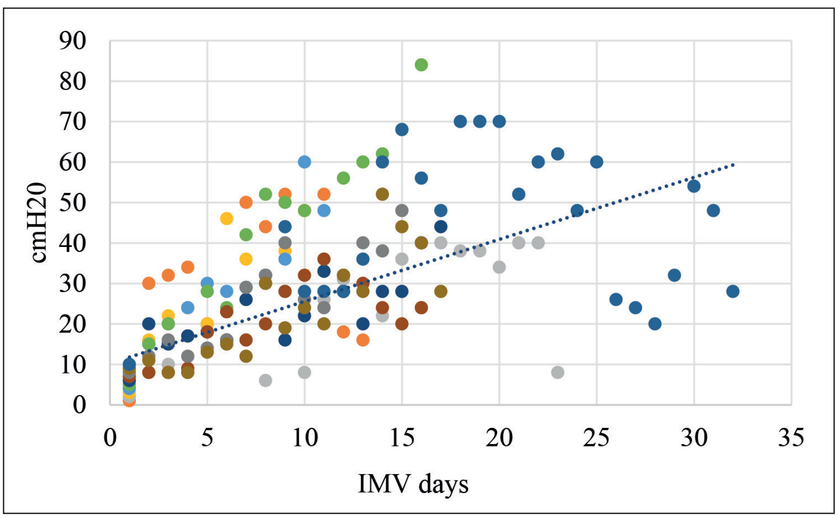

Figure 2. Maximum expiratory pressure. Individual daily values of maximum expiratory pressure during invasive mechanical ventilation. Each patient is represented by a different color. Daily values represent the average of three measurements per infant (N=10). IMV: Invasive Mechanical Ventilation.

MIP and MEP

An improvement in MIP values was observed during consecutive daily measurements, reaching a significant difference between baseline and final values for the 10 patients (-24.3 ± 12.44 and -46 ± 6.93, respectively). MEP showed similar behavior, with baseline values significantly lower than final values (mean 16 ± 6.78 and 43.4 ± 17.18, respectively) (table 2). However, in 4 children, decreasing MEP values were observed on the last days of MV, and in one child, it reached lower values than the initial values on the 7th day of MV. This was not the case with MIP values, which remained rising throughout ventilatory support (figures 2 and 3). In addition, although there were only two female infants, their MIP values on the last day of MV were lower than those obtained in the male infants.

Discussion

This study shows that respiratory muscle strength estimated by DE, MIP, and MEP improved during MV of infants with severe botulism.

Right and left DE values measured daily increased as neuroparalysis progressed. Although values associated with successful extubation in infants with botulism have not been reported, all patients in our series exceeded the cut-off points predictive of successful extubation by Yao et al. of 0.8 cm for children aged 1 to 3 years[17] and by Abdel et al. of 0.6 cm in infants, children, and adolescents[18]. However, Arslan et al. found a mean right DE of 1.4 ± 0.4 cm, with a sensitivity of 87% and specificity of 81.2 % in successful extubation of school-aged children, similar to the values found in adults[19], which was only reached by two infants with

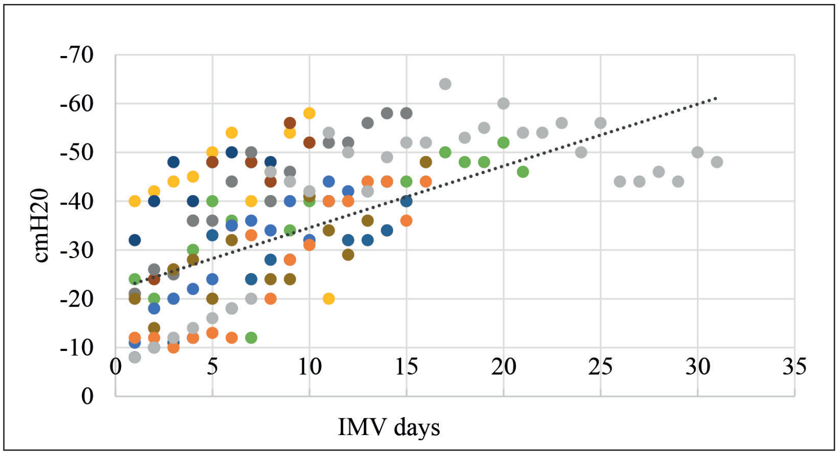

Figure 3. Maximum inspiratory pressure. Individual daily values of maximum inspiratory pressure during invasive mechanical ventilation. Each patient is represented by a different color. Daily values represent the average of three measurements per infant (N=10). IMV: Invasive Mechanical Ventilation.

botulism at the time of extubation. 70% of our patients obtained values > 0.6 cm on the first day of IMV, which is described to be close to the 50th percentile in healthy infants weighing < 10 kg[20]. This suggests that infants require different cut-off points, given the age-dependent diaphragmatic anatomical variations, which are evidenced in ultrasound with DE values that progressively increase from birth to adolescence[13,20].

Additionally, multiple papers describe the relationship of diaphragmatic ultrasound with clinical progression, but most exclude children with neuromuscular weakness, where values may be much lower[21]. Besides, we found discordance between right and left DEs in 4 of our patients; however, the cause could not be established. Differences in the anatomy and motion of both hemidiaphragms are well known, with a ratio of up to 1:1.7 cm (left:right) in healthy, mechanically ventilated adult patients. This value tends to be consistent and supports the practical recommendation of using the right side for measurement, as it provides a better acoustic window[22]. Hemidiaphragmatic excursion may vary in the presence of muscle dysfunction, changes in intra-abdominal pressure, or lung compliance. In our patients, this variability could have been further influenced by inter-operator differences or uneven diaphragmatic involvement due to botulinum toxin[23]. The characteristics of the pulmonary parenchyma must also be considered; its ultrasound evaluation determines the success of extubation with a high predictive value[18]. In addition, decreased lung compliance significantly affects the patient's capacity to generate inspiratory volume and therefore decreases DE[24]. Infants with severe botulism usually require MV due to diaphragmatic weakness, although sometimes they present parenchymal complications such as atelectasis, pneumonia due to bronchial aspiration, among others.

Regarding MIP, there are few data on the values related to successful extubation in children. In Argentine patients, MIP values between 30-35 cmH_2O were observed during SBT, with no differences between those who failed or succeeded in extubation[25]. However, Khemani et al. reported respiratory muscle weakness with a risk of extubation failure of 14% with MIP ≤ 30 cmH_2O, which rises to 40% if post-extubation stridor is also considered[26]. 80% of our patients had MIP < 30 cmH_2O on the first day of ventilatory support but managed to rise to > 45 cmH_2O the day before extubation. Although these are low pressures relative to those found in neonates with successful extubation [MIP 65 (16-125) cmH_2O][10], they are similar to those found during maximal effort in infants with neuromuscular weakness[27]. This age-related variability in MIP is associated with limited patient cooperation and the immaturity of respiratory muscles at early ages. Xue proposes adjusting MIP values to body weight to overcome this bias, finding that values ≥ 0.86 cmH_2O/kg are associated with successful extubation, with a sensitivity of 51% and specificity of 82%[28]. Our patients achieved extubation with lower MIP values, but which, in relation to body weight, are higher (mean 6 ± 0.9 cmH_2O/kg). This could indicate different cut-off points in infants with botulism. Strikingly, in this study, we found on the last day of MV an increase in MIP of 47% (mean 21.7 cmH_2O) and in MEP of 63% (mean 27.4 cmH_2O), compared to the day of admission. This gap is not reported in other studies but could be a more reliable marker than those found in isolation during SBT. In addition, we found lower MIP values in female patients, which could be related to hormonal and muscle growth factors[29].

The MEP values of our patients were higher than 37 ± 12 cmH_2O, reported during exertion in children with neuromuscular diseases[27] and similar to those found in neonates with successful extubation [38 cmH_2O (6.56-121)][10]. The decrease in final MEP observed in 4 children was not associated with extubation failure, and may have been due to poor secretion management, abdominal muscle weakness, circuit leaks, among other factors. The infants maintained values higher than baseline during the final days, highlighting the usefulness of MEP monitoring in assessing the recovery of muscle strength.

Finally, during the study period, 56 cases of infant botulism were reported in Argentina[30], of which 16 corresponded to the Mendoza province. The sample of this study represents 20% of the cases in Argentina, given the high incidence of this pathology in our region. Local conditions allowed a rapid confirmatory diagnosis by mouse bioassay, which is delayed up to 6 times longer in other Argentinean centers[31]. The mean number of days of stay in PICU and MV was similar to that reported in other centers in the groups that received botulinum antitoxin[32]. The finding of higher DE values in patients with longer MV, hospitalization, and PICU stay could be related to a delay in extubation due to causes other than muscular ones.

Limitations

The small sample size hinders generalization of the results, and the absence of extubation failure did not allow estimation of a cut-off point for successful extubation. In addition, the retrospective design limited data collection. First, infants had IMV for a mean of 15 days; this time is prolonged and may be associated with ventilator-related diaphragmatic dysfunction, which was not evaluated[28]. Nutritional status plays an important role in muscle strength. Body mass index was not assessed and is valuable in children for adjusting both airway pressures and diaphragmatic ultrasound[33]. Second, MIP and MEP measurements can vary significantly with minute volume, hypercapnia, and endotracheal tube leaks[34,35]. These variables were not controlled, nor was it ensured that MIP measurements were performed at minimal residual volume, for example, by using a pneumotachograph. The analog one-way occlusion device used in this study may be associated with lower MIP values than the actual ones[36]. Third, the impact of the SBT on the outcomes is unknown, as patient-ventilator synchrony, dead space, circuit resistance, and other factors, which could be detrimental in children with neuromuscular weakness, were not documented[37].

Conclusion

To our knowledge, this is the first work that analyzes clinical and ultrasound variables of respiratory muscles in infants with severe botulism. DE, MIP, and MEP values improved daily, reaching significant differences from admission to IMV until the day before extubation in infants with severe botulism. Although there were no patients with extubation failure, these parameters could be included in a clinical assessment bundle to detect the timing of MV weaning in this population with neuromuscular weakness. Further studies are needed to establish cut-off points and determine the usefulness of these tools.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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