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Non-Invasive Ventilation for Acute Respiratory Failure in Duchenne Muscular Dystrophy Patients

Ventilación no invasiva para la insuficiencia respiratoria aguda en pacientes con distrofia muscular de Duchenne

Dear Editor:

Duchenne Muscular Dystrophy (DMD) is the most common inherited muscle disease in children, with a prevalence ranging between 1.3 and 2.1 per 10,000 live male births.[1] Acute Respiratory Failure (ARF) is a common complication in individuals with DMD and a primary cause of mortality, both in the teenage and adult years.[2]

Non-Invasive Ventilation (NIV) is a ventilatory technique for delivering pressurized gas to the lungs through a sealed mask that can be placed over the mouth, nose or the whole face; its utilization is recommended for the management of ARF across a variety of aetiologies. However, NIV application in exacerbated DMD patients is still controversial and not indicated by major guidelines.[3] The aim of our study was to evaluate clinical status and outcomes in DMD patients being administered NIV for ARF.

We collected and reviewed all of the medical records of the DMD patients with ARF who were admitted to our adult 4 bed Respiratory ICU (RICU) at the University of Padua Medical Center between January 1, 2005 and December 31, 2019. Ethical approval was waived by the local Ethics Committee in view of the fact that the study was retrospective and not prepared according to a research project.

At the time of admission to the RICU, the clinical and physiologic parameters of these patients were consistent with ARF. In particular, each of them presented at least one of the following: (1) respiratory distress; (2) hypoxemia and/or hypercapnia; (3) acute respiratory acidosis.[4] Patients who had received NIV as first-line ventilatory treatment were included in the study; those who had a tracheostomy tube in place or showed an immediate need for Endotracheal Intubation (ETI)[5] were excluded.

All hospital charts were reviewed for patients' baseline clinical, demographic and pulmonary function data after informed consent release forms were obtained. Clinical, laboratory and blood gas data at RICU admission were also recorded and analyzed.

Causes of ARF were classified as: upper respiratory tract infection (URTI); acute decompensated heart failure (ADHF); pneumonia; and other (e.g., pneumothorax, pulmonary thromboembolism, dysphagia with aspiration, gastroparesis/malnutrition, acute gastrointestinal distension, abuse of sedatives). The diagnosis of URTI was based on the presence of one or more of the following symptoms or signs: fever, throat irritation or sore throat, hoarseness[6]; the diagnoses of pneumonia and/or ADHF were based on major guidelines.[7,8]

The decision to begin NIV was usually made by the attending physician, according to the hospital internal protocol.[9] NIV was usually delivered using a portable ventilator set in assisted pressure-control ventilation (APCV) mode. A commercial full-face mask was used when NIV was initiated and in some cases it was substituted by a nasal mask after the first hours of ventilation. In the event of NIV failure, the patients were shifted from NIV to Invasive Mechanical Ventilation (IMV) by ETI unless they had previously declared that they did not wish to be intubated. Mechanical In-Exsufflation (MI-E) was usually administered to those patients showing bronchial mucous encumbrance and oxyhemoglobin desaturation secondary to secretion retention, according to the hospital internal protocol.[6] The patients were divided into 2 groups depending on their NIV response. "NIV success group" was made up of those individuals who avoided ETI, were discharged from RICU and survived for at least 48 h after being transferred to the respiratory ward. "NIV failure group" was made up of those subjects who required ETI or died while on NIV support.

During the study period, 51 patients were admitted to our RICU for ARF with a primary diagnosis of DMD. Seven (13.7%) had a tracheostomy tube in place and were administered IMV via tracheal cannula, 2 (3.9%) were intubated at admission, while all the remaining 42 (82.3%), received NIV as the first-line ventilatory intervention and were considered eligible to participate in our retrospective study. No patient experienced repeated episodes of ARF. Of notice, RICU admissions were evenly distributed during the study period. Baseline demographic, clinical, pulmonary and cardiac function, of the patients are outlined in Table 1. Conditions associated with the onset of ARF in the patients studied included URTI (19 cases); ADHF (5 cases); pneumonia (4 cases); and other conditions (14 cases). The patients were administered NIV in APCV. The initial inspiratory pressure above PEEP was 12 (8–25) cmH$_2$O. All subjects were fully cooperative during NIV and did not require any sedation. NIV was successful in 36 patients (85.7%), while unsuccessful in the remaining 6 (14.3%). The median time from NIV initiation to intubation was 3.5 (1–11) days. Among patients who failed NIV, the cause of ARF was dysphagia with aspiration in 3 cases; ADHF in 2 cases; and pneumonia in 1 case. Causes of NIV failure were failure to adequately correct hypercapnia and exhaustion (3 cases), persistent accumulation of bronchial secretions (2 cases), and severe hemodynamic instability (1 case). Two patients died following intubation while on IMV support; the remaining four required tracheostomy due to difficult weaning and underwent long-term invasive ventilation. No major NIV complication was observed, while minor complications occurred in 4 patients (nasal skin lesions in 3 cases and acute bowel distension in 1 case). All 36 patients successfully treated and 4 out of 6 who failed NIV were discharged alive from hospital. Patients' characteristics at RICU admission are outlined in Table 1. The median survival of the 42 NIV patients after RICU admission was 67.1 (95%CI, 15.0 to 125.4) days. Survival was significantly reduced for patients who failed NIV, compared to those who succeeded [median survival time: 11.7 (95%CI, 0.0 to 131.0) vs 85.9 (95%CI, 24.9 to 125.4) days], with an HR of dying of 3.91 (95%CI, 1.10 to 13.93; $p = 0.0351$). None of the covariates had a significant effect on NIV failure. However, patients who did not respond to NIV were younger than those who succeeded [15 (14–30) vs. 24.5 (14–41) yrs; $p = 0.0201$]; moreover, patients' characteristics at RICU admission showed greater HR values [123.0 (120.0–134.0) vs. 104.0 (45.0–112.0) b/min; $p = 0.0095$], total WBC count [13.2 (11.06–17.80) vs. 8.65 (2.06–18.02); $p = 0.0113$] and SaO$_2$ [98 (94.8–99.2) vs. 95.1 (88.9–99); $p = 0.011$] for failures, as opposed to successes (Table 1).

Table 1
Patients' baseline demographic, clinical, and cardio-pulmonary function characteristics, and clinical, laboratory and blood gas data at RICU admission.

	All cases	NIV succes group	NIV failure group	p-Value
Baseline demographic, clinical and cardio-pulmonary function data				
Number of subjects	42	36 (85.7%)	6 (14.3%)	NA
Age (years), median (range)	23.5 (2–41)	24.5 (14–41)	15 (14–30)	0.0201
BMI (kg/m²), median (range)	21.1 (9.5–35.2)	21.1 (9.5–35.2)	20.7 (14.7–28.5)	0.9615
Age at DMD diagnosis (years), median (range)	5 (0.3–11)	5 (0.3–11.0)	0.7 (0.7–0.7)	0.1932
Pts with scoliosis, N (%)	37 (88.1)	33 (91.7)	4 (66.7)	0.1414
Pts with cardiomyopathy, N (%)	19 (45.2)	17 (47.2)	2 (33.3)	0.6729
Pts with a history of constipation, N (%)	10 (23.8)	9 (25.0)	1 (16.7)	0.9999
Pts undergoing long-term NIV, N (%)	19 (45.2)	17 (47.2)	2 (33.3)	0.6729
Pts previously administered PEG, N (%)	6 (14.3)	5 (13.9)	1 (16.7)	0.9999
FVC (L), median (range)	0.86 (0.11–1.98)	0.85 (0.11–1.98)	0.96 (0.30–1.47)	0.8967
FVC (%), median (range)	16.0 (3.0–96.0)	15.0 (3.0–96.0)	22.0 (9.0–32.0)	0.9501
MIP (cm H₂O), median (range)	23 (8–37)	23 (8–37)	–	NA
MEP (cm H₂O), median (range)	20 (4–30)	20 (4–30)	–	NA
Clinical, laboratory and blood gas data at RICU admission				
Heart rate (beats/min), median (range)	108.5 (45.0–134.0)	104.0 (45.0–112.0)	123.0 (120.0–134.0)	0.0095
Respiratory rate (breaths/min), median (range)	14.0 (12.0–18.0)	14.0 (12.0–18.0)	14.0 (12.0–16.0)	0.8390
Pts with fever, N (%) (Temperature >38 °C)	3 (7.1)	3 (8.3)	0 (0.0)	0.9999
Total WBC count (×10⁹/L), median (range)	8.82 (2.06–18.02)	8.65 (2.06–18.02)	13.2 (11.06–17.80)	0.0113
Pts with abnormal CRP or ESR level, N (%)	15 (35.7)	14 (38.9)	1 (16.7)	0.5085
PaO₂ * (mmHg), median (range)	71.6 (33.8–175)	70.6 (43.1–105.8)	92.8 (33.8–175)	0.2123
PaCO₂ (mmHg), median (range)	44.7 (31.6–96.1)	44.6 (32–78)	52.8 (31.6–96.1)	0.5949
Arterial pH, median (range)	7.4 (7.3–7.6)	7.4 (7.3–7.6)	7.4 (7.3–7.5)	0.8698
SaO₂ (%), median (range)	95.5 (88.9–99.2)	95.1 (88.9–99)	98 (94.8–99.2)	0.0110
Pts with abnormal BNP or NT-proBNP level, N (%)	13 (30.9)	12 (33.3)	1 (16.7)	0.6468
Pts with hypokalemia, N (%)	12 (28.6)	10 (27.7)	2 (33.3)	0.9999

BMI = Body Mass Index; BNP = Brain Natriuretic Peptide; CRP = C-Reactive Protein; DMD = Duchenne Muscular Dystrophy; ESR = Erythrocyte Sedimentation Rate; FVC = Forced Vital Capacity; MEP = Maximal Expiratory Pressure; MIP = Maximal Inspiratory Pressure; NA = not applicable; NIV = Non-Invasive Ventilation; NT-proBNP = N-terminal pro-hormone of Brain Natriuretic Peptide; PEG = Percutaneous gastrostomy; RICU = Respiratory Intensive Care Unit; SaO₂ = arterial oxygen saturation; WBC = White Blood Cell).
p-Values refer to differences between NIV success and NIV failure groups.
  * During supplemental oxygen therapy.

The use of NIV in DMD patients for ARF is still debated.[10–12] In our study, the overall success rate of 86% corroborates the positive role of NIV in avoiding tracheal intubation. On our opinion, high success rate of NIV treatment in our patients can be explained by several factors, including the following. First, we used APCV, a mode of partial ventilatory support found to be comfortable and minimally affected by patient–ventilator asynchrony in individuals with ventilatory failure of neuromuscular origin.[13] Second, we chose full-face mask as first choice. Indeed, nasal masks may be problematic in these patients because of weakness of masseter muscles, causing incomplete jaw closing and major mouth air leaks. Furthermore, patients with ARF are characterized by mouth-breathing making nasal masks ineffective. For these reasons, despite a potentially increased risk of gastric distension and emesis into the mask,[14] a full face mask was preferred in our patients. Third, the combined use of MI-E was effective in clearing bronchial secretions in most patients who developed bronchial mucous encumbrance and consequent oxyhemoglobin desaturation, in keeping with previous data both in adults and children with NMD.[15] Finally, it is worth remarking that our team of pulmonary physicians and nurses has been involved in NIV treatment of NMD patients with ARF for over 20 years.

Notwithstanding the low NIV failure rate, we believe that appropriate selection criteria for attempting NIV in this setting is a crucial unresolved issue. Unfortunately, we found none of the covariates associated with NIV failure. Noteworthy, patients who did not respond to NIV were younger than those who succeeded and reported dysphagia, weight loss and aspiration in 3 out of 6 cases. Swallowing disturbances resulting in increased risk of inhalation have been reported as a possible mechanism of ARF in boys with DMD[16] and a common cause of NIV failure in NMD patients.[9]

Of interest, there was a trend toward higher PaO₂, SaO₂, and PaCO₂ values in the NIV failure compared to NIV success group. We hypothesize that delivery of excessively high amounts of supplemental oxygen during transfer to our RICU might have increased the risk of NIV failure, by depressing spontaneous ventilation. Indeed, oxygen therapy has been shown to reduce the drive to breathe and lead to CO₂ retention in DMD patients during respiratory exacerbations.[17]

Our study has important limitations, being single-centered, retrospective and observational. It is important to remind, however, that prospective randomized trials in this patient population are unlikely to be performed because of the limited number of patients affected with DMD and of possible ethical issues. The study's long time span is also a potential weakness. Worth mentioning, however, we did not make significant changes in pharmacologic therapy and/or supportive care during the study period.

Despite these major limitations, our study indicates NIV to be a viable option in DMD patients showing signs of ARF as it can effectively reverse ARF in the majority of patients, with the caveat that its use should be extremely careful in younger patients with dysphagia.

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Síndrome de absceso hepático y bronconeumonía por *Klebsiella pneumoniae* hipermucoviscosa

Liver Abscess Syndrome and Hypermucoviscous Klebsiella pneumoniae *Bronchopneumonia*

Estimado Director:

Klebsiella pneumoniae es una bacteria gram negativa que forma parte de la flora intestinal de personas sanas, causante raras veces de infección extrahospitalaria en pacientes con factores de riesgo, y con mayor frecuencia de infecciones nosocomiales urinarias y respiratorias. En 1986 Liu et al. describieron un nuevo síndrome causado por *Klebsiella pneumoniae*, consistente en un absceso hepático asociado a endoftalmitis séptica, cuadro grave e invasivo causado por serotipos capsulares K1 o K2, asociada a un fenotipo de hipermucoviscosidad e hipervirulencia denominado síndrome de absceso hepático (SAHK)[1]. En 2004 Fang et al. identificaron el nuevo gen *magA* en aislamientos de un nuevo microorganismo hipervirulento del SAHK, cuya característica principal es causar infección grave en individuos jóvenes e inmunocompetentes[2]. Presentamos el caso de un paciente afecto de SAHK acompañado de bronconeumonía bilateral grave, proceso raramente descrito en nuestro país.

Varón de 70 años natural de Argelia y residente en España, sin haber viajado recientemente. Exfumador de 16 paquetes/año, diabético tipo 2, con cardiopatía isquémica crónica, sin antecedentes neumológicos, en tratamiento con atenolol, ramipril y metformina. Acudió a urgencias por fiebre de 3 días de evolución, asociado a náuseas y dolor pleurítico derecho. A la exploración presentaba regular estado general, se encontraba taquipneico con 22 rpm, con O_2 en cánulas nasales a 4 l/min tenía una SaO_2 de 95%, tensión arterial de 100/50 mm Hg, frecuencia cardiaca de 85 lpm, encontrándose febril con una temperatura de 39 °C. La auscultación pulmonar presentaba crepitantes hasta los campos medios bilaterales. Se le realizó una radiografía de tórax en la que se observaron infiltrados periféricos en ambos hemitórax, compatibles con bronconeumonía (fig. 1 A).

En las pruebas complementarias de urgencias destacaba gasometría arterial (FiO_2 0,21): pH 7,44; $PaCO_2$ 31 mm Hg, PaO_2 53 mm Hg, HCO_3 20,9 mmol/l, PaO_2/FiO_2 252; analítica con leucocitos 8.310/ml, neutrófilos 77%, linfocitos 8,1%; hematíes 4.100.000/ml; hemoglobina 12,2 g/dl; hematocrito 33%; plaquetas 119.000/ml; índice de Quick 68%; dímero D 1.772 ng/ml, glucosa 280 mg/dl, urea 42 mg/dl; creatinina 1,46 mg/dl; albúmina 2,40 g/dl; sodio 130 mmol/l; potasio 3,50 mmol/l; ALT 143 U/l; LDH 281 U/l; proteína C reactiva > 25 mg/dl. El sedimento de orina fue normal. La PCR de SARS CoV-2 fue negativa. A las 48 horas los hemocultivos mostraron crecimiento de *Klebsiella pneumoniae* multisensible. El urocultivo y la antigenuria para *Legionella* y neumococo fueron negativos. A las 24 horas el paciente presentó hipotensión, mayor taquipnea, Tª 38 °C y empeoramiento radiológico, con infiltrados parcheados en progresión bilateral. En la TAC toracoabdominal destacaba derrame pleural bilateral asociado a múltiples infiltrados alveolares nodulares, patrón en empedrado en ambos ápex y segmentos anteriores de ambos lóbulos superiores con defectos de repleción en arterias pulmonares lobares bilaterales. Se observaban 2 lesiones focales heterogéneas compatibles con abscesos hepáticos, de 8,8 × 6,5 cm y de 2 cm, tromboembolismo pulmonar agudo periférico bilateral, sin signos de sobrecarga derecha, y émbolos sépticos (fig. 1 B), ingresando en la UCI ante la mala evolución presentada. La ecocardioscopia mostró FEVI 60% sin dilatación de cavidades derechas. Mediante ecografía Doppler de extremidades inferiores se descartó trombosis venosa profunda.

Se realizó punción y drenaje percutáneo del absceso hepático, aislando en el cultivo *Klebsiella pneumoniae*, serotipo capsular K1, fenotipo hipermucoviscoso, multisensible y resistente a ampicilina