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ORIGINAL ARTICLE

Predictors of upper airway obstruction following extubation in critically ill children

Predictores de obstrucción alta de vías respiratorias posterior a la extubación en niños graves

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

In the pediatric population, airway obstruction following extubation is the most frequent complication, mostly caused by extubation failure. Despite this, there is no strong evidence regarding risk factors or prevention strategies.

What does this study contribute to what is already known?

In a cohort of 260 critically ill patients, 25% presented high airway obstruction after extubation. This complication was associated with being an infant and the duration of MV of less than or equal to 3 days.

Abstract

Upper airway obstruction after extubation is a serious complication that can lead to extubation failure and other unfavorable outcomes in children. **Objective**: to describe the incidence and risk factors associated with post-extubation upper airway obstruction in critically ill children. **Patients and Method:** A prospective descriptive observational study was carried out in a pediatric intensive care unit in Argentina over two years. Patients older than 1 month and younger than 18 years, receiving mechanical ventilatory support (MV) for more than 24 hours through an endotracheal tube (ETT) and with at least one programmed extubation were included. **Results**: Of 260 patients, 65 (25%) developed post-extubation upper obstruction. Of them, 37 were females (56.9%), with a median age of 14 months and 10 kg weight. The PIM3 score was 2.8 and the most frequent reason for admission was acute lower respiratory infection in 38 (43.1%) patients, among whom 36 (55.4%) had at least one complex chronic condition. Twenty-seven (41.5%) failed extubation and 5 (7.7%) required tracheostomy. A multiple logistic regression analysis was performed to determine the relationship between different variables with the dependent variable. Independent risk factors explaining post-extubation upper obstruction were age ≤ 24 months and MV support for ≤ 3 days. **Conclusion**: Post-extubation upper airway obstruction is frequent in the pediatric intensive care unit. We found that infants and mechanical ventilation duration less than or equal to 3 days are independent risk factors for its presentation.

Keywords:
Airway Obstruction;
Artificial Respiration;
Extubation;
Intensive Care Unit;
Stridor

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Introduction

Post-extubation upper airway obstruction (UAO) is a common and potentially serious complication in pediatrics that can lead, among other things, to extubation failure[1,2]. In general, post-extubation UAO manifests clinically with inspiratory effort, muscle retraction, and stridor that can appear acutely or gradually in the first hours after extubation[3]. This clinical picture is generally due to the lumen reduction of the extra-thoracic airway, which increases resistance to inspiratory flow and increases the work of breathing (WOB) that, depending on its severity, can induce respiratory failure requiring reintubation[4,5].

Most studies mentioning post-extubation UAO are related to extubation failure and associated complications. There is little research focusing on the risk factors and evolution of post-extubation UAO within the pediatric intensive care unit (PICU)[6-9]. The prevalence of post-extubation UAO reported in PICUs varies between 15-41%.

Many methods have been described for its diagnosis, where the most objective methods to assess WOB are calibrated respiratory inductance plethysmography (RIP) and esophageal manometry, used in centers where there is clinical research and advanced monitoring resources are available; however, the most widely used method is clinical evaluation. One of its problems is the subjectivity of the health professional in detecting stridor, its severity, and differentiating supraglottic from subglottic disease, but its strength is that it is always available and no additional monitoring elements are required[2,6,10-14].

The evolution of post-extubation UAO is a little studied and variable phenomenon that generally evolves in a benign way requiring only minimal pharmacological interventions such as steroids, nebulized adrenaline, or inhaled corticosteroids[12,15-18]. In the most severe cases, non-invasive ventilation (NIV) is usually used to stabilize the upper airway using positive airway pressure. Therefore, the intraluminal pressure of the upper airway is maintained above the critical closing pressure avoiding its collapse and, at the same time, helping the fatigued respiratory muscles[19-22]. However, there is no evidence so far that NIV prevents reintubation due to UAO. The most frequent reason for extubation failure in PICUs is upper obstruction, increasing days of analgosedation, hospitalization, mechanical ventilation (MV), need for tracheostomy, and mortality[7,23,24].

The primary objective of this study is to identify the risk factors for post-extubation UAO and its prevalence, and secondarily to describe the population that develops it.

Patients and Method

Single-center prospective descriptive observational study, conducted at the *Hospital Nacional de Pediatría Juan P. Garrahan*, Ciudad Autónoma de Buenos Aires, Argentina, between January 1, 2016, and December 31, 2017. This hospital is a pediatric High Complexity center with 534 beds (132 for pediatric care) and all pediatric specialties. The multipurpose PICU has 17 beds with an approximate annual admission of 500 patients.

Patients older than 1 month and younger than 18 years, with MV > 24 hours through an endotracheal tube (ETT), and who were extubated at least once on a scheduled basis were included in the study. Only unplanned extubations were excluded as well as patients in whom post-extubation UAO-related data were not obtained.

For data collection, an electronic database was designed to record the following variables grouped into 3 categories:

1. Demographics: age (months), sex, weight (kg); Pediatric index of mortality (PIM) 3[25]; mortality; days of hospitalization; diagnosis at admission: lesion or traumatic injury in any area of the body that requires admission to PICU (polytrauma, head trauma, gunshot wound, near drowning, poisoning, burns, electrocution); acute respiratory distress syndrome ARDS in the healthy child without complex chronic disease (CCD) (bronchiolitis, pneumonia, ARDS with CCD, post-surgical, neurosurgical, immunocompromised, non-respiratory infection, acute neurological event, neuromuscular disease, other); CCD (respiratory, neurologic, oncologic, cardiac, other)[26]; neurological injury at extubation (evaluable from abnormal dynamics of airway protection mechanisms unrelated to sedatives)[27].
2. Airway and MV: ETT with or without cuff; ETT size according to the Cole's formula (age in years/4 + 4) for ETT without cuff and modified Cole's formula for ETT with cuff (age in years/4 + 3.5); days of ETT; tracheostomy (TCT) requirement record; reason for TCT; standardized weaning process: progressive lowering of ventilatory support along with the performance of a daily 30-minute spontaneous breathing test using T-tube, achieving extubation if the test was successful; post-extubation UAO: presence of stridor post-extubation, with accessory muscles recruitment requiring some type of intervention either pharmacological, non-invasive or invasive MV due to this obstructive event[16,28,29]; clinical evaluation: performed by the intensivist and the physiotherapist responsible of extubation; days of MV; spontaneous breathing

test; prone ventilation; ARDS[30]; failure of extubation; reason for failure (upper obstruction, respiratory center disturbances, muscle fatigue, lack of airway protection mechanisms, others).

3. Post-extubation non-invasive ventilation (NIV): implemented bilevel and synchronized within the first 2 hours post-extubation with intermediate category equipment (Trilogy 202®, Philips Respironics, Eindhoven, The Netherlands); Dräger Carina®, Lübeck, Germany); type of interface (cannula, nasal pillows, nasal mask, oronasal mask, full face mask); NIV success/failure; type of failure (initial: 0-2 hours, early: 2-12 hours, late: > 12 hours)[31]; reason for NIV failure (hypoxemia, hypercapnia, respiratory distress, decreased sensorium, failed airway protection, upper obstruction, others).
(*Supplementary Figure* describing the operational definitions of the variables recorded available in the online version).

Statistical Analysis

Variables were reported as mean and standard deviation (SD) or median and interquartile range 25-75 (IQR) as appropriate to their distribution. Categorical variables were reported as number of presentation and percentage.

The Kolmogorov-Smirnov test was used to determine the sample distribution. Univariate logistic regression analysis was performed to determine the relationship between different variables with the dependent variable "upper obstruction post-extubation". To compare continuous variables, the Student's t-test or Mann-Whitney U-test was used, as appropriate. To compare categorical variables, the Chi-square test or the Fisher's exact test was used. Multiple logistic regression analysis was then performed to determine the relationship between different variables with the dependent variable. The backward stepwise regression method was used.

To control for potential confounding factors, those variables with a possible association ($p < 0.10$) in the univariate analysis were included in the analysis. As a measure of association, adjusted Odds Ratios (OR) with their corresponding 95% confidence intervals were reported. The goodness-of-fit and model accuracy was analyzed using the Hosmer-Lemeshow test and the area under the ROC curve. A p-value < 0.05 was considered significant. IBM SPSS software® Macintosh, version 24.0 (IBM Corp., Armonk, NY, USA) was used for data analysis.

For quality control, missing data related to the post-extubation UAO variable had to be discarded, representing less than 10%. There would not appear to be a consistent pattern of data loss in the patient records, limiting the potential bias related to them.

Throughout the entire process, the confidentiality of the data and the preservation of the patient´s identity was guaranteed by numerical coding.

This study was approved by the Hospital Ethics Committee of the *Hospital de Pediatría "Prof. Dr. Juan P. Garrahan"*.

Results

During the study period, 964 patients were admitted to the PICU, of whom 364 received MV and 260 were included in the study. Figure 1 shows the causes of exclusion and patient flow. The median age was 19.5 months, and 143 (55%) patients were less than 2 years old. The median weight was 11.7 kg and the most frequent diagnosis was ARDS in patients with CCD in 54 (20.8%) cases (table 1). The ETT diameter used was 4-4.5mm (table 2). 54 (20.8%) patients failed extubation.

65 patients developed post-extubation UAO, 37 (56.9%) were females, with a median age of 4 months (2-14) and a median weight of 10 kg (6-12). The PIM 3 was 2.8% and the most frequent reason for admission was due to ARDS in 38 (43.1%) patients among whom 36 (55.4%) had at least one CCD (table 1). Of the patients who developed post-extubation UAO, 27 (41.5%) failed extubation. Five of them (7.7%) required tracheostomy due to airway disorders (4 subglottic stenosis and 1 vocal cord paralysis) (*Supplementary Table* available in the online version). Of the 38 (58.5%) patients with post-extubation UAO who did not fail extubation, 13 (20%) required NIV with a median of 2 days.

Table 1 shows the bivariate analysis of post-extubation UAO according to the variables analyzed. Table 3 shows the multivariate logistic regression analysis, which was controlled by the following variables: age ≤ 24 months, body weight ≤ 12 kg, Vt/PP ≤ 10 ml/kg, ETT internal diameter ≤ 4.5mm, and cuffed airway and MV duration ≤ 3 days. In our population, age ≤ 4 months [OR 4.2 (95%CI 2.1 to 8.1); $p < 0.001$] and MV duration ≤ 3 days [OR 2.1 (95%CI 1.1 to 4.0); $p < 0.029$] resulted in independent risk factors for post-extubation UAO. The area under the curve of the model was 0.68 [95% CI = 0.61 - 0.75], indicating low predictive ability.

Discussion

The main result of our study is the identification of age ≤ 24 months and MV duration ≤ 3 days as independent variables associated with post-extubation UAO. Also, we determined a 25% frequency of post-extubation UAO in a heterogeneous population of critically ill children with MV.

The literature mentions a greater number of risk factors for extubation failure than for post-extubation UAO, possibly due to the close association between them. The incidence of extubation failure due to post-extubation UAO described internationally ranges from 25-50%[7,9,12]. The prevalence of post-extubation UAO described in the literature is highly variable and may be due to different reasons. Some studies exclude airway surgeries and patients with upper airway injuries from the analysis[13,14] while others include specific populations such as cardiovascular surgery patients, neurocritical patients, preterm newborns, or just patients undergoing anesthesia recovery[2,28,32-35]. This evidences that the clinical scenarios studied are diverse, which leads to such variability. However, our study provides data on clinical-surgical patients with a reason for admission characterized by a high frequency of patients with acute respiratory infection (39% of cases).

Similar to that reported by Kurachek et al, the highest proportion of patients (60%) had at least one CCD, which could be because our study was carried out in a highly complex center in Latin America and a reference center in Argentina. Although CCD makes patient management difficult, due to their pathological characteristics and previous morbidities, could characterize a population *a priori* at higher risk of developing post-extubation UAO. Clinical investigations, like our study, report the absence of statistical association between post-extubation UAO and CCD[2,8].

Some studies only mention post-extubation UAO associated with severe events such as extubation failure and tracheostomy requirement, excluding from the analysis other cases of post-extubation UAO because they are considered perhaps less severe[7,8]. However, in the last five years, publications describe a high prevalence percentage, showing that one in four patients requiring endotracheal intubation could develop post-extubation UAO, ranging from 18.5 to 26%[6,11,13,24,29].

Although the implementation of a standardized definition could have contributed to the identification of post-extubation UAO, its high frequency could undoubtedly be associated with the use of ETT with cuff. Their use avoids situations that increase the risk of airway injury, such as the implementation of leak reduction strategies usually performed with uncuffed ETTs, associated with the use of larger diameter ETTs, while reducing the times an ETT needs to be replaced[36]. In addition, we could observe, as other authors, that the use of cuffed ETT was not associated with an increase in post-extubation UAO, possibly associated with the monitoring of cuff pressure with manometry in our center without exceeding 25 mmHg, since, as described by Deakers et al, the use of ETT with cuff does not appear to be a risk factor for post-extubation stridor in pediatric patients, if the necessary precautions are taken to control the pressure of the cuff[37,38].

Concerning the above, there is controversy as to

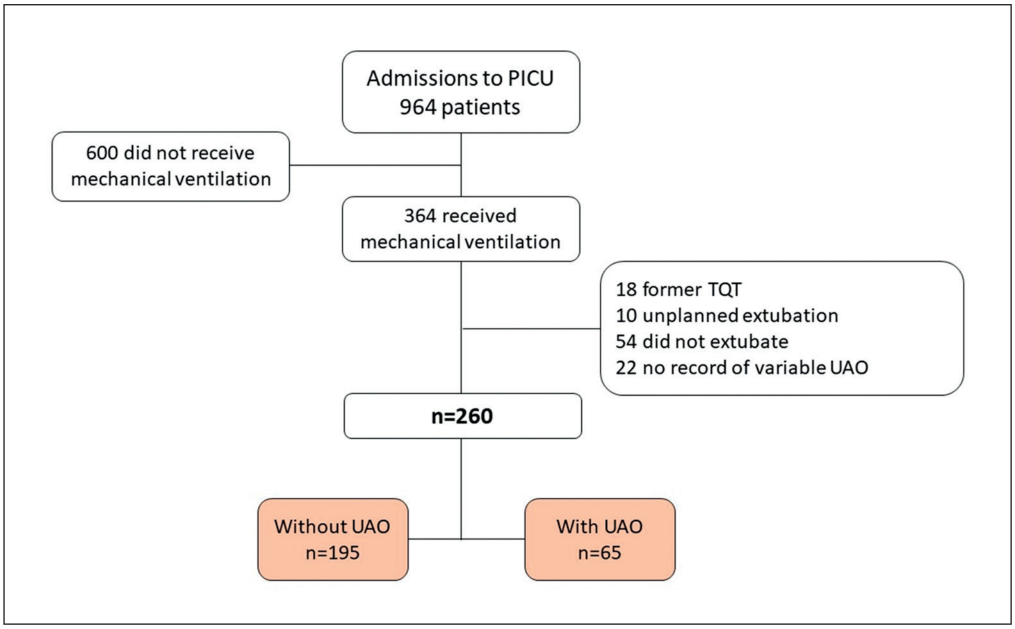

Figure 1. Flow chart of patients included in the study. PICU: pediatric intensive care unit; TQT: tracheostomy; UAO: upper airway obstruction

Table 1. Clinical and demographic characteristics of the cohort and cases, according to the presence of upper airway obstruction after extubation

	All (n = 260)	Without UAO (n = 195)	With UAO (n = 65)	p Value
Female gender, n(%)	159 (61.2)	122 (62.6)	37 (56.9)	0.42
Age (months) , median (RIQ)	19.5 (7-99.7)	28 (9-119)	4 (2-14)	0.001
Weight, median (RIQ), kilograms	11.7 (7-24)	12 (7-30)	10 (6.15-12)	0.001
PIM 3, median (RIQ)	2.8 (0.8-5.3)	2.8 (0.8-5.8)	2.8 (0.7-3.9)	0.16
Mortality, n (%)	4 (1.53)	4 (2.05)	0	0.25
Lenght of stay in PICU, median (RIQ)	13 (9-19)	13 (9-18)	13 (9-21.5)	0.93
Diagnosis, n (%)				N/A
- Trauma	11 (4.2)	7 (3.6)	4 (6.2)	0.47
- Respiratory disease (without CCD)	46 (17.7)	31 (15.9)	15 (23.1)	0.19
- Post-surgical	40 (15.4)	27 (13.8)	13 (20)	0.23
- Neurosurgical	25 (9.6)	18 (9.2)	7 (10.8)	0.72
- Inmunocompromised	5 (1.9)	5 (2.6)	0 (0)	0.34
- Respiratory disease (with CCD)	54 (20.8)	41 (21)	13 (20)	0.86
- Non-respiratory infection	20 (7.7)	16 (8.2)	4 (6.2)	0.59
- Acute neurological event	26 (10)	20 (10.3)	6 (9.2)	0.81
- Neuromuscular disease	9 (3.5)	7 (3.6)	2 (3.1)	1.0
- Others	24 (9.2)	23 (11.8)	1 (1.5)	0.013
CCD, n (%)	160 (61.5)	124 (63.6)	36 (55.4)	0.24
- Respiratory	27 (10.4)	23 (11.8)	4 (6.2)	0.20
- Neurologic	58 (22.3)	43 (22.1)	15 (23.1)	0.86
- Oncologic	16 (6.2)	14 (7.2)	2 (3.1)	0.37
- Cardiac	8 (3.1)	5 (2.6)	3 (4.6)	0.42
- Others	51 (19.6)	39 (20)	12 (18.5)	0.78
Neurological injury at extubation, n (%)	59 (22.7)	43 (22.1)	16 (24.6)	0.67
Endotracheal tuve with cuff, n (%)	186 (71.5)	148 (75.9)	38 (58.5)	0.007
Internal diameter of ETT, median (RIQ), mm	4.5 (4-5.5)	4.5 (4-6)	4 (3.5-4.5)	0.001
Prone position, n (%)	32 (12.4)	23 (11.8)	9 (13.8)	0.66
ARDS, n (%)	29 (11.2)	22 (11.3)	7 (10.8)	0.91
Days of use of muscle relaxants, median (RIQ)	1 (0-3)	1 (0-3)	1 (0-2)	0.40
Days of MV, median (RIQ)	6 (3-9)	6 (4-10)	5 (3-8)	0.10
MV > 21 days, n (%)	19 (7.3)	14 (7.2)	5 (7.7)	1.0
Spontaneous breathing trial, n (%)	240 (92.3)	179 (91.8)	61 (93.8)	0.59

UAO: Upper Airway Obstruction; PICU: Pediatric intensive care unit; CCD: chronic complex disease; ETT: endotracheal tube; ARDS: acute respiratory disease syndrome; MV: mechanical ventilation.

Table 2. Distribution of sizes and type of endotracheal tube according to age

	All n = 260	< 12 months n = 89	12-23 months n = 52	≥ 24 months n = 119
ETT size, n(%)				
- 3-3.5 mm	54 (20.8)	50 (56.2)	3 (5.8)	1 (0.8)
- 4-4.5 mm	111 (42.7)	39 (43.8)	43 (82.7)	29 (24.4)
- 5-5.5 mm	35 (13.5)	n/a	6 (11.5)	29 (24.4)
- ≥ 6 mm	60 (23)	n/a	n/a	60 (50.4)
TET con balón "SI", n (%)	186 (71.5)	54 (60.7)	24 (46.2)	108 (90.8)

ETT: endotracheal tuve l; mm: milimeters; n/a: not applicable.

Table 3. Results of the logistic regression analysis for Upper Airway Obstruction after extubation

	OR (IC 95%)	p value
Age ≤ 24 months	4.17 (2.14 - 8.11)	< 0.001
Length of mechanical ventilation ≤ 3	2.08 (1.08 - 4.00)	0.029

Area under the curve: 0.68 [IC al 95% = 0.61-0.75]. Test de Hosmer y Lemeshow p = 0.96.

which is the best method of cuff pressure control in pediatric patients.[39]. Shaikh et al. recently suggested that protocolized cuff pressure monitoring may not be the most efficient way to reduce post-extubation stridor and proposed a clinical method of "minimal leak" that would allow pressure monitoring through auscultation of the leak, which would not only reduce the number of checks but also dispense with the use of a specific and expensive cuff measurement device.

Khemani et al. argue that one of the reasons why there is so much inconsistency in finding risk factors, effective treatments, and preventive measures for post-extubation UAO is the weakness of clinical interpretation by professionals in its diagnosis[40]. However, there is evidence that the absence of post-extubation stridor is a clinical sign that could rule out subglottic stenosis[3,40]. In our study, where we used clinical evaluation as a diagnostic method, the percentage of patients with post-extubation UAO is similar to that reported in another study where the authors evidenced the presence of post-extubation UAO using a physiological tool specifically developed for clinical research, such as esophageal manometry combined with impedance plethysmography, which is hardly available in other areas[6]. Therefore, we could come to consider that a clinical method, carried out by a group of expert professionals, although less objective than the one proposed by Khemani, could be reliable for the detection of post-extubation UAO. In relation to their findings, Nascimiento et al. suggested the future need to analyze age as a possible risk factor for the occurrence of post-extubation UAO due to the anatomy and physiology of young infants[14]. Consistent with this, we found that age younger than 2 years is a risk factor associated with post-extubation UAO. This could be related to the anatomical and structural characteristics of the pediatric airway. This factor, in addition to the presence of subglottic edema, favors the decrease of the internal diameter of the airway but, as the airway develops, this event stops happening, in general after 18 months of age[6].

The selection of the ETT size is an issue to be highlighted since the growth of the pediatric population is very uneven. As a starting point, Cole's formula is implemented as a selection method, but then the size of the patient and the decision of the treating physician must be considered in order to avoid leaks and optimize ventilation. The difficulty in keeping intubated young children quiet in relation to MV time could also contribute to the development of lesions that favor the presence of post-extubation UAO in this population[6]. About this, Green et al. described as a risk factor for post-extubation UAO the need for postoperative sedation in intubated patients, arguing that this could be due to the presence of agitation and excessive movement of the patients, which exposes the airway to trauma and consequent inflammation[2].

Other authors did not find an association with post-extubation UAO in relation to the prolonged use of MV[38], but the use of MV between 24-72hs has been described as a risk factor[14]. This coincides with our results in identifying as an independent risk factor associated with post-extubation UAO the use of MV for a period less than or equal to 3 days. Associated with this, we cannot ignore the presence of a frequent situation such as positive fluid balance in this population during the first 24-72 hours of MV that is related to greater complications associated with MV and to a greater risk of developing subglottic edema, which would favor the risk of post-extubation UAO[41,42].

Among the limitations of our study, we can consider that the post-extubation UAO clinical diagnostic method, despite being the most widely used in publications on this subject, is not the most objective. However, our professional team is highly trained in this method so the risk of error could be low. On the other hand, we did not record some variables that could modify the risk of post-extubation UAO, such as those related to intubation (number of attempts or trauma during the procedure), leakage around the ETT, use of corticosteroids, and sedation at the time of extubation. However, although with a model of low predictive power, we have found two risk factors for post-extubation UAO in our study population.

We know that external validity is limited because the study was conducted in a single center, however, we present a sample of significant size and representative of patients with diverse pathologies as it is common to find in multipurpose pediatric intensive care, especially being this the case of a Latin American reference hospital, where both patients without comorbidities and others of greater complexity are admitted.

Conclusion

This study allowed us to know and provide a regional prevalence value of post-extubation UAO of 25%

in our center, similar to that reported in other world reference centers. We also identified that infants and duration of MV less than or equal to 3 days are independent risk factors for post-extubation UAO. We consider these findings to be essential for improving the process of weaning patients from MV and a starting point for future research on the subject.

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.

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