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LARYNGOLOGY

Association of endotracheal tube repositioning and acute laryngeal lesions during mechanical ventilation in children

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Abstract The objective of this study is to determine the incidence of post-extubation acute laryngeal lesions in a pediatric intensive care unit (PICU) and potential risk factors. Children, aged 28 days to 5 years, admitted to the PICU who required endotracheal intubation for at least 24 h were enrolled. Exclusion criteria were a previous intubation, history of laryngeal disease, current or past tracheostomy, the presence of craniofacial malformations and patients considered on palliative care. All patients underwent flexible fiber-optic laryngoscopy (FFL) not later than 8 h after extubation. A blinded researcher identified and classified laryngeal lesions based on recorded media. 231 children were enrolled between November 2005 and December 2015. At FFL examination, 102 children (44.15%) presented moderate to severe laryngeal lesions. On a multivariable analysis, we found that for each additional day with repositioning of the endotracheal tube, there was an increase of 7.3% (RR 95% CI 1.012–1.137; $P = 0.018$) on the baseline risk of developing moderate to severe acute laryngeal lesions. Furthermore, for each additional dose of sedation per day of intubation, there was also an increase of 3.5% on the same baseline risk (RR 95% CI 1.001–1.070; $P = 0.041$). The amount of tube repositioning episodes and the need for extra doses of sedation (as a proxy for possible agitation) were found to be associated with acute laryngeal lesions. Adequate sedation and minimized tube repositioning should be pursued to possibly prevent the development of post-extubation airway compromise.

Keywords Intubation · Laryngoscopy · Laryngostenosis · Artificial ventilation

Introduction

Acquired subglottic stenosis (SGS) is a clinical entity well recognized since 1965, when the use of prolonged endotracheal intubation started to be used for newborns who required ventilator support for longer periods [1]. Histopathological studies conducted on pediatric patients have shown that large and deep ulcerations caused by the contact of the endotracheal tube (ETT) with the mucosa of the upper airway stimulate the production of collagen and the development of fibrous scar tissue. This scar tissue slowly shrinks causing posterior glottic and subglottic stenosis [2, 3].

In this context, SGS is the final result of an acute laryngeal damage, which is a direct consequence of tube contact and overpressure on airway mucosa. Therefore, acute laryngeal lesions are recognized as a key factor predicting the development of SGS [4]. However, not all patients presenting with acute lesions eventually progress to chronic ones. Which subgroup of patients ultimately develops SGS and what risk factors potentiate this outcome are still important questions to be answered.

On the other hand, the assessment of the development of acute airway lesions themselves after intubation, and the

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way that potential risk factors interact in its onset, could possibly contribute to the understanding of the pathogenesis, while possibly making way for early interventions. The interruption of this initial step may decrease the long term risk of SGS, and thus preventing the need for complex laryngotracheal reconstruction [5, 6].

An established risk factor for SGS pathogenesis is sedation. Children maintained at an inadequate level of sedation during endotracheal intubation period seem to develop higher rates of chronic lesions [7, 8], possibly through ETT mobilization trauma, especially during agitation episodes. Also, duration of intubation plays a role in SGS, augmenting the risk of outcome for those in prolonged use of ETT [8]. Whether these or other parameters also play a role in acute laryngeal lesions has not been systematically tested in a prospective study yet.

To clarify these research gaps, the objective of the present study was to determine incidence of post-extubation acute laryngeal lesions in a pediatric intensive care unit and assess potential risk factors.

Patients and methods

All patients undergoing endotracheal intubation in the Pediatric Intensive Care Unit (PICU) of Hospital de Clínicas de Porto Alegre (HCPA) were evaluated for eligibility. Inclusion criteria were age between 28 days and 5 years and intubation requirement for more than 24 h. Patients were considered not eligible if they had a history of dysphonia or stridor, prior intubation, current or past tracheostomy or craniofacial malformations (this information was collected with parents or caregivers to exclude conditions that could pose important biases, as they could result in undiagnosed SGS before intubation). Also, those considered in palliative care by the PICU staff were also excluded, as it would be unethical to burden those patients with research procedures while discussing end-of-life terms with the family. Informed consent was obtained from parents or guardians before children were enrolled in the study. This study was approved by the institutional research ethics committee under the project number 05-266.

Parents were interviewed within the first 24 h of admission to the PICU to collect data regarding pregnancy, comorbid conditions, and previous hospitalizations. Data concerning the diagnosis and intubation procedures, such as number of attempts, level of training of the physician performing the procedure (resident or staff critical care pediatrician), size of endotracheal tube (ETT), and the presence or absence of cuff, were obtained from the medical staff.

During their stay in the PICU, children were monitored daily for events like repositioning of ETT (whether advancement or pulling back the ETT, according to hemithoraces auscultation, radiological images or ventilation parameters), number of reintubations, need for sedation increment, or use of additional doses of sedatives to maintain the desired level of sedation.

Concerning the PICU routines, all intubation procedures (except for those demanding an urgent approach) followed a protocol of fast intubation sequence, with the use of midazolam, fentanyl, and rocuronium. Tube size was determined based on guidance from the American Heart Association [9], and manufacturers were Portex (Portex Limited, Kent, UK) or Rusch (Teleflex Medical, North Carolina, USA) industries. Tube size adequacy was evaluated by the difference of inspiratory and expiratory tidal volumes, as measured by the PICU assistant physician; tube size was considered adequate when there was a difference of 20–25% between the two measured volumes. If the difference was greater than that or the clinical condition was itself severe enough to require higher ventilatory parameters, then the tube size was changed or a cuffed tube was used, according to the opinion of the PICU assistant physician. When a cuffed tube was used, the insufflation pressure of the cuff was measured by the PICU staff nurse and kept under 20 cm of H_2O. Tube fixation was performed with an appropriate adhesive bandage and tube fixation and dead space checking was performed on each shift (three times a day). Those on mechanical ventilation were maintained sedated with midazolam (0.2 mg/kg/h) and fentanyl (2 mcg/kg/h) infusion, continuously. Humidification of inhaled gases was performed during the whole period of ventilatory support.

Endoscopic evaluation

Patients underwent flexible fiber-optic laryngoscopy (FFL) on the first 8 h after extubation, with an Olympus ENF-P4 fiber-optic laryngoscope (Olympus, Tokyo, Japan), with an outer diameter of 3.4 mm, with no side channel for suction or biopsy. The fiber-optic laryngoscope was connected to a Storz® microcamera and a Stryker Vision Elect® video monitor, and examinations were recorded in a Panasonic DVD recorder DMR-ES15LB-S (Manaus, Brazil). Whenever aspiration of luminal secretions was necessary during examination, a parallel suction probe was inserted through nasal or oral route.

Examinations were performed at bedside in the PICU without sedation by one of five main investigators (D.M., C.S.N., C.S., L.V.E., D.R.P.), all of which were otolaryngologists. Patients were positioned across the bed, without neck hyperextension, maintaining oximetry and cardiac monitoring. As the examinations were performed on the

first hours after extubation, all patients received supplemental oxygen via nasal cannula, maintained during the procedure. After positioning, the patient was immobilized by the nursing staff, and a lidocaine hydrochloride 2% gel was applied around the endoscope surface. FFL was advanced to the supraglottic region, aiming for supraglottic, glottic and subglottic images. Complications were immediately recorded after the examination. Minor complications included desaturation to 85% with rapid recovery, mild nasal bleeding, and laryngospasm not requiring positive pressure ventilation. Desaturation below 85%, bradycardia, and laryngospasm requiring intubation or positive pressure ventilation were considered severe complications.

A senior laryngologist (G.K.), blinded to patient clinical data, was responsible for evaluating lesions from endoscopic examinations video recordings. Examination findings were classified into two groups (Table 1), according to criteria from Classification of Acute Laryngeal Injuries (CALI) [4], which we have adopted institutionally, and that was recently formally validated showing a distinctive prediction attribute for chronic lesions:

- Group 1: encompassed normal examinations and those patients with mild lesions (edema, hyperemia, hemorrhage, and nonobstructive laryngomalacia);
- Group 2: patients presenting moderate to severe lesions (laryngeal immobility, obstructive laryngomalacia, ulceration, and granulation of the posterior glottic or subglottic tissue).

All children were followed up after extubation and discharge from the PICU, and checked for symptoms and signs of respiratory distress such as stridor, tachypnea and subcostal or suprasternal retraction. Patients enrolled in this cohort were followed up after discharge from PICU and the development of chronic lesions was sought actively or conservatively depending on the group of lesions presented at the first examination. Data on chronic lesions are published elsewhere [4, 7, 8, 10].

Statistical analysis

Continuous variables were not normally distributed according to Shapiro–Wilk test, and therefore described as median and interquartile range (IQR). Categorical variables were described as absolute (n) and relative (%) frequency. A univariable regression model was used to select parameters for a multivariable final model, using robust estimation Poisson regression. For the final multivariable model to be constructed, we have used all parameters showing an association with the outcome with a P value of 0.2 or less in the univariable model and also those considered clinically significant, and posteriorly we followed a backward stepwise approach to exclude non-significant variables from the final model. Model assumptions for linearity of residuals and goodness-of-fit were assessed for the univariable and multivariable models. Multicollinearity of final predictors was assessed through VIF and tolerance parameters. Variance inflation factor (VIF) and tolerance are related parameters that represent the amount of variance of an estimated regression coefficient that is increased because of collinearity. Interaction between final predictors was also tested for significance. Proportions between groups were compared using the Pearson Chi-square test or Fisher's exact test. A significance level of 5% was considered. Statistical analysis was performed on SPSS 20.0.0.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Results

Between November 2005 and December 2015, a total of 278 patients were considered eligible for the study. Written consent was obtained from parents or caregivers of 270 children. From these, three patients underwent tracheostomy for prolonged mechanical ventilation and 36 died during hospitalization (before any FFL examination could be performed). Those patients were considered loss to our study (14.4%) and their data have not been

Table 1 Description of laryngeal abnormalities observed on post-extubation flexible fiber-optic laryngoscopy

Anatomical region	Mild	Moderate	Severe
Supraglottic	Edema	Obstructive LM	
	Hyperemia		
	Non-obstructive LM		
Glottic	Edema	Uni- or bilateral ulceration	Vocal fold paralysis
	Hyperemia	Arytenoid granulation	IA ulceration
			IA granulation
Subglottic	Edema	Partial ulceration	Complete ulceration
	Hyperemia		Granulation

IA interarytenoid, *LM* laryngomalacia

evaluated. Two hundred and thirty-one patients completed the study and could were included in the final analysis.

Median age was 2.87 months, ranging from 0.6 to 59.5 months, and 135 patients (58.4%) were male. Causes of intubation were as follows: bronchiolitis (142 cases, 61.5%), pneumonia (35 cases, 15.2%), other respiratory diseases (15 cases, 6.5%), meningitis (14 cases, 6.1%), and 25 cases (10.8%) had miscellaneous diagnoses. Oral route for intubation was preferred in the majority of cases (230 patients, 99.6%). Only one patient demanded nasotracheal intubation.

The median time between extubation and baseline FFL was 5 h and 20 min (IQR: 15 min to 7 h). Three children had oxygen desaturation reaching 85%. Desaturation resolved without intervention, and all the procedures could be completed. Only one child had hemoglobin saturation reduced to 75%. This was resolved after the use of a venturi mask, without the need for reintubation. At that time, the procedure had already been conducted, and the results could be properly analyzed. On FFL, 88 patients (43.6%) had moderate or severe acute laryngeal lesions and 114 (56.4%) had a normal examination or mild abnormalities.

Adequate visualization of the subglottic region (360°) was achieved in 161 patients (80.1%) and partially achieved in 31 patients (15.4%). Subglottis was not visualized in nine patients (4.5%). Three of these had obstructive laryngomalacia and six had glottic granulation tissue. These patients were followed up, and another examination was conducted within 7–10 days.

Risk factors for acute laryngeal lesions

Association of several potential predictors and the more severe spectrum of laryngeal lesions (Group 2) was evaluated. Distribution of variables in Groups 1 and 2, relative risk for acute laryngeal lesions and significance level on univariable analysis are shown in Table 2.

We have considered clinically relevant variables based on a previous study [8] added to variables with a P value lower than 0.2, in the univariable analysis, to build the final multivariable model. The final model is shown in Table 3.

In this regression model, we found that for each increase in one extra dose of sedation per day, there was a mean increase of 3.5% in the risk of a moderate to severe laryngeal lesion, while for each additional day of ETT repositioning there was a mean increase in 7.3% in the risk of the same outcome. All other factors were excluded from the final model due to non-significant associations. Both predictors showed irrelevant collinearity test results (VIF <10 and tolerance >0.1). The interaction term between predictors in the final model was also insignificant ($P = 0.826$).

Discussion

Endotracheal intubation is one of the commonest invasive procedures in PICUs and it is associated with different degrees of damage to the laryngeal mucosa [11]. The pathophysiology of severe lesions suggests that there is a sequence of events that culminates in sequelae to the airway [5, 12]. Serious damages, such as subglottic stenosis, develop from basic lesions, such as ulcers and cartilage exposure. This process is possibly influenced by patient-related factors and to the intubation procedure itself. The latter factors are of great interest because they are potentially amenable to intervention. Therefore, defining these risk factors clearly must be pursued so that management planning could be more effective in preventing unfavorable outcomes [13].

Table 2 Univariable analysis of potential risk factors for acute laryngeal lesions

Variable	Moderate to severe acute lesions ($n = 102$)	Normal larynx or mild abnormalities ($n = 129$)	Relative risk of acute laryngeal lesion	95% CI	P value
Age (months)	3.52 (1.77–10.09)	2.57 (1.64–6.07)	1.01	0.99–1.02	0.29
Male (%)	57 (55.9%)	78 (60.5%)	1.11	0.83–1.48	0.48
Gestational age (weeks)	38 (36–40)	37 (35–39)	1.04	0.99–1.10	0.10
Intubation attempts	1 (1.0–1.0)	1 (1.0–1.0)	0.97	0.83–1.13	0.69
Reintubations	0 (0–1.0)	0 (0–1.0)	0.98	0.79–1.22	0.85
Days of intubation	6.5 (5.0–9.0)	7 (5.0–10.0)	0.99	0.97–1.03	0.95
Extra doses of sedation/DI	9.07 (6.23–10.8)	7.86 (4.71–10.75)	1.03	0.99–1.06	0.07
Use of cuffed ETT	29 (28.7%)	25 (19.5%)	0.87	0.56–1.04	0.08
Total ETT repositioning days	1 (0–3)	1 (0–2)	1.06	1.002–1.124	0.04

Data is described as n (%) or median and interquartile range

ETT endotracheal tube, *RR* relative risk, *DI* days of intubation

Table 3 Multivariable final model

Variable	Relative risk	95% CI	*P* value
Extra doses of sedation/DI	1.035	1.001–1.070	0.041
Total ETT repositioning days	1.073	1.012–1.137	0.024

ETT endotracheal tube, *DI* days of intubation

We have adopted FFL as a main examination approach in this study. Indeed, rigid fiber-optic laryngoscopy with general anesthesia and spontaneous ventilation could provide more detailed information on laryngeal lesions. However, in this study all children were assessed after extubation regardless of symptomatology, thus the use of general anesthesia was not warranted in this setting. Recently, a study from our group showed that FFL has a sensitivity of 93.7% and a negative predictive value of 98.8% when performed to screen post-extubation laryngeal lesions [8]. In addition, Smith et al. identified a rate as low as 2.4% of minor complications (desaturation with rapid recovery and/or mild epistaxis). Thus, the use of bedside FFL seems to be a safe and practical screening method to assess airway lesions [14].

We found an incidence of intubation-associated moderate to severe lesions of 44.15%, comparable to other reported cohort results. Cordeiro et al. [13] reported an incidence of 34.9% of moderate to severe lesions in neonates and children and Fan et al. [15], 43% in newborns. We emphasize that our sample is made up of post-neonatal children only, a different population from the aforementioned studies. So far as we know, this is the largest prospective study including exclusively PICU patients.

The presence of acute laryngeal lesions, especially those classified as moderate to severe, is an isolated predictor of the development of SGS. In a prospective study from our group, including 123 PICU patients undergoing endotracheal intubation, we found an incidence rate of 11.38% of SGS [10] and all children who developed SGS had moderate to severe abnormalities on the after extubation FFL, demonstrating a remarkable sensitivity on this first assessment.

Although several risk factors have been observed to be associated with laryngotracheal lesions, the relative relevance of these factors is still unclear [11]. In chronic lesions, we found that the duration of mechanical ventilation and the need for extra doses of sedation (as a proxy for agitation and attrition of the mucosal wall to the ETT) are important risk factors for the development of SGS during endotracheal intubation [8]. Cordeiro et al. identified the need for reintubation and exchange of ETT as risk factors for the development of moderate to severe lesions [13]. The development of post-intubation lesions is probably a multifactorial phenomenon.

In this study, it was found that both ETT repositioning (proportion of days with ETT repositioning over the total of days intubated) and extra doses of sedation have a statistically significant association with the development of moderate to severe acute laryngeal lesions in a multivariable analysis. Radiological studies show that the ETT can move up to 3.8 cm while repositioning the head from flexion to hyperextension. The sole inspiratory movement elicits a repetitive cephalocaudal movement of the larynx that can lead to significant damage when ETT is in place [16]. Bishop, in 1989, had already suggested that ETT mobilization and pressure on the airway mucosa causing abrasion and necrosis are both hypothetic factors for the development of laryngeal lesions [12]. Therefore, strategies to avoid or to minimize ETT mobilization must be pursued in the care of the mechanically ventilated patient.

Although the association of the use of extra doses of sedation with SGS has been demonstrated earlier, its influence on acute laryngeal lesions had not until now been reported. A greater amount of rescue doses of sedatives seems to imply a higher level of agitation, determining an augmented risk of ETT rubbing the airway mucosa [7]. Independence of variation was a possible issue and both predictors could show collinear behaviors, but this was excluded by collinearity tests. Also, interaction between predictors was not found in the final model.

While facing these results with other publications on the subject, an important negative finding must be addressed. The length of intubation was previously shown to be an important risk factor for SGS [8], but this predictor was not associated with acute laryngeal lesions in this analysis. On the other hand, ETT mobilization was not important in the establishment of chronic lesions [8], but had a great impact on the development of acute laryngeal lesions. At this point, we can only infer why this counterintuitive behavior could be explained.

It is known that chronic lesions develop over the course of acute laryngeal lesions, but there are only a proportion of those acute lesions that effectively end up leading to SGS. Therefore, although common risk factors should exist for both conditions (as we have shown here with "extra doses of sedations per day of intubation"), it would not be unusual if some risk factors could pertain solely to one or another outcome. Based on our findings, we could argue that while agitation/inadequate sedation are a universal risk factor for laryngeal lesions, the mobilization of ETT influences basically the precipitation of mucosal damage. Whether this established damage would persist and progress to overt SGS, must be the result of aggregation of additional risk factors, one of them clearly the duration of intubation.

Conclusion

We found a significant incidence of post-extubation acute laryngeal lesions in this cohort of patients. Moderate to severe lesions were positively associated with the amount of extra doses of sedation received and the amount of ETT mobilizations, even after controlling for substantial confounding variables and other potential risk factors. Based on these findings, judicious mobilization of ETT is advised in children, at least those under 5 years of age, while the level of sedation should be cautiously set up to avoid periods of agitation.

Compliance with ethical standards

Funding This study has not received funding from any kind from any institution.

Conflict of interest All authors declare no conflict of interest of any kind.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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