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Resolution of vocal fold immobility in preterm infants☆

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ABSTRACT

Introduction: Vocal fold immobility (VFI) is an important sequela of preterm birth due to patent ductus arteriosus (PDA) ligation and invasive ventilation. A minority of these patients experience VFI resolution. The purpose of this study is to determine factors associated with VFI resolution in preterm infants.
Methods: This is a case control study of preterm (< 37 weeks gestation) infants admitted to a metropolitan Level IV neonatal intensive care unit from 2006 to 2012. All patients diagnosed with VFI by flexible nasolaryngoscopy were divided into 2 cohorts: those with and without laryngoscopic resolution of VFI during follow-up. Univariate and multivariate analyses were performed to determine factors associated with VFI resolution.
Results: Of 71 patients with VFI and adequate follow-up, 17 (23.9%) experienced resolution. Median (range) follow-up was 25.7 (0.4–91.3) months and time to resolution 4.4 (0.4–38.8) months. Compared to the ongoing-VFI cohort, those who experienced resolution had higher median gestational age (31 vs 25 weeks, p = 0.006) and birth weight (1550 vs 765 g, p = 0.02), and lower likelihood of undergoing PDA ligation (47.1% vs 77.8%, p = 0.02). On multivariate analysis, history of PDA ligation remained independently associated with a lower likelihood of VFI resolution (p = 0.02, OR 0.2, 95% CI 0.1–0.8). Among PDA ligation patients, birth weight > 1000 g was more common in the resolution cohort compared to the ongoing-VFI cohort (62.5% vs 24.4%, p = 0.047).
Conclusion: While lower birth weight and gestational age are known risk factors for VFI following PDA ligation, in this study, these factors were also associated with a decreased likelihood of VFI resolution. Furthermore, PDA ligation appears to be a risk for both the development and persistence of VFI. This evidence should inform prognosis and intervention decisions for preterm infants with VFI.

1. Introduction

1.1. Background

Vocal fold immobility (VFI) has long been recognized as one of the most common neonatal laryngeal anomalies [1,2]. The risk of VFI for preterm infants due to patent ductus arteriosus (PDA) ligation has been well documented [3–5], and children with preterm birth history are more likely than their full-term peers to develop childhood dysphonia [6–8]. Our recently published study reported that in a cohort of surviving preterm infants from a single level IV neonatal intensive care unit (NICU), 3.5% developed VFI, most commonly associated with a history of PDA ligation and/or invasive ventilation [9].

In the largest cohort of pediatric VFI patients, resolution of immobility was noted in only 28% of patients with adequate follow-up [10]. Similarly in a cohort of exclusively preterm infants with VFI, only 24% demonstrated resolution on repeat flexible nasolaryngoscopy (FNL) [9]. The majority of those who do not experience resolution have ongoing symptoms related to immobility and high rates of surgical interventions [9,10].

1.2. Objectives and hypotheses

The purpose of this project was thus to further analyze the cohort of preterm infants with VFI from our recent study and compare those with resolution to the remainder that did not recover mobility, in order to determine what factors were associated with resolution. Specifically, we hypothesized that the cohort with resolution would have a lower likelihood of iatrogenic immobility, and a higher median birth weight and gestational age. A secondary aim was to separately analyze the

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patients whose VFI was due to PDA ligation to determine if any identified factors remained significant in this subset. Elucidating factors associated with resolution can help inform caregiver counseling related to prognosis as well as provider decision-making regarding intervention in preterm patients with VFI.

2. Methods

2.1. Population

This is a case control study involving all surviving preterm infants (< 37 weeks gestational age) seen in the NICU at Children's Hospital of Wisconsin (CHW) between January 1, 2006, and September 1, 2012, who developed VFI. The study was approved by the institutional review board at CHW. The CHW NICU is a level IV facility in a metropolitan setting, and patients were included in the cohort whether they were born at the affiliated Froedtert Hospital Birth Center or transferred from an outside facility. Patients with more than one NICU stay were counted once each.

2.2. Data acquisition

Patients were defined as having VFI by chart review revealing a diagnosis of unilateral or bilateral, partial or complete "Paralysis of Vocal Cords or Larynx" (*International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes 478.31–478.35). All such diagnoses were made by FNL performed or overseen by 1 of 8 attending pediatric otolaryngologists. FNL was performed in consultation when a patient's symptoms (most commonly a weak cry or dysphagia) raised concern for potential airway pathology. At the time of the study period, FNL was not routinely performed preoperatively for PDA ligation patients or even postoperatively in the absence of symptoms. Patients were included in the study whether the initial FNL diagnosing VFI was performed during their NICU stay or afterward (e.g., in the step-down unit or cardiovascular intensive care unit). Follow-up was defined as at least 1 repeat evaluation by the pediatric otolaryngology team greater than 1 week from initial diagnosis. Those without adequate follow-up were excluded. Follow-up included repeat FNL while still inpatient if there was a significant change in symptoms, or more commonly, outpatient follow-up in the otolaryngology clinic 1–3 months from discharge. With rare exception, repeat FNL exams for each patient were performed by the attending pediatric otolaryngologist who performed or supervised the original diagnostic FNL. Resolution was defined as documentation on repeat FNL of return of normal mobility in a previously immobile vocal fold.

2.3. Statistical analysis

The total VFI population was thus split into 2 cohorts: those with documented resolution, and the control cohort with ongoing immobility. The cohorts were compared regarding demographic factors, gestational age, birth weight, etiology and laterality of immobility, history of PDA ligation, and history of invasive ventilation. Univariate analysis was performed using chi-squared, Fisher exact, Mann-Whitney, and 2-tailed t-tests. Multivariate analysis was then performed of all significant factors using multiple logistic regression.

3. Results

A total of 73 patients developed VFI, 2 of whom were excluded for lack of follow-up information, leaving 71 for inclusion in the study. Of those, 17 (23.9%) demonstrated resolution during the study period, at a median time of 4.4 (0.4–38.8) months. Median follow-up for all 71 patients was 25.7 (0.4–91.3) months, with follow-up significantly longer in the ongoing immobility compared to resolution group (30.5 vs 4.4 months, p < 0.001).

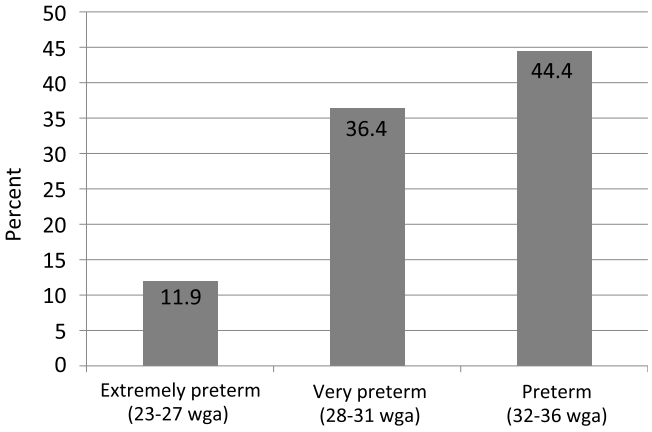

Fig. 1. Percent of patients at each gestational age who achieved resolution. Significant difference between youngest and oldest cohorts (p = 0.01). Wga = weeks gestational age.

Compared to the ongoing-VFI cohort, the resolution cohort had significantly higher median gestational age (31 vs 25 weeks, p = 0.006) and birth weight (1550 vs 765 g, p = 0.02). A distribution by age is shown in Fig. 1. There was no significant difference in laterality (p = 0.77) or etiology (p = 0.08) of immobility between the 2 groups. Immobility at least partly attributed to iatrogenic injury was present in 9 (52.9%) resolution and 41 (75.9%) ongoing-VFI patients (p = 0.07). The resolution cohort was less likely than the ongoing-VFI group to have been diagnosed with PDA (52.9% vs 87.0%, p = 0.03) and undergone PDA ligation (47.1% vs 77.8%, p = 0.02). The likelihood of undergoing ligation once diagnosed with PDA was no different between the resolution and ongoing cohorts (88.9% and 89.4% respectively, p = 1). Ventilation history (defined as a history of at least 1 day of invasive ventilation not related to a procedure) was not significantly different between the groups (12 [70.6%] resolution vs 39 [72.2%] ongoing-VFI patients [p = 0.83]). Full results of univariate analysis between the 2 groups are in Table 1.

On initial multivariate analysis, neither gestational age < 26 weeks (p = 0.75, OR 0.7, 95% CI 0.1–5.1), birth weight < 1000 g (p = 0.26, OR 0.4, 95% CI 0.1–2.1), nor history of PDA ligation (p = 0.09, OR 0.3, 95% CI 0.1–1.2) were significantly associated with VFI resolution independently. However, after controlling for presumed interaction between gestational age and birth weight, history of PDA ligation was independently associated with lower likelihood of resolution (p = 0.02, OR 0.2, 95% CI 0.1–0.8).

Fifty patients (8 resolution and 42 ongoing) were included in separate analysis involving only those with PDA ligation history. In this subgroup, median gestational age and birth weight were not significantly different between the resolution cohort and ongoing-VFI patients (27.5 [24–36] vs 25 [23–36] months, p = 0.09; 1243 [660–2890] vs 710 [450–4065]g, p = 0.10). The only significant difference was a lower proportion of extremely low-birth weight patients (< 1000 g) in the resolution compared to ongoing-VFI cohort (37.5% vs 75.6%, p = 0.047). Full results of this comparison are in Table 2.

4. Discussion

4.1. Relevant literature

The importance of VFI in the preterm population has been indirectly recognized for several years in multiple papers examining VFI in PDA ligation patients [3–5,11]. However, only more recently has the broader question of VFI in preterm patients at large (regardless of PDA ligation status) been examined. For instance, several papers demonstrated the higher rate of childhood dysphonia in preterm patients compared to their term peers [6–8]. These studies did not address VFI