Incidence and causes of prolonged mechanical ventilation in children with Down syndrome undergoing cardiac surgery

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Introduction: Trisomy 21 is the most common syndrome in children with a 30–50% association with congenital heart disease (CHD). Cardiac surgeries are required in the majority of Down syndrome (DS) with CHD cases. Because of the distinctive abnormalities in their respiratory system, children with DS may require longer positive pressure ventilation after cardiac surgery. The aim of this study is to investigate the incidence and possible risk factors for prolonged mechanical ventilation (PMV) need in DS patients undergoing cardiac surgery.

Methods: We conducted a prospective study on all DS children who underwent cardiac surgery from 2013 to 2016. Demographic and perioperative data were collected including the duration of mechanical ventilation, respiratory risk factors such as previous infection, evidence of pulmonary hypertension during the intensive care unit (ICU) stay, the presence of lung collapse, secretion and wheezy chest, inotropes score, sedation score, arrhythmias, and low cardiac output syndrome. Based on the duration of mechanical ventilation, cases were divided into two groups: the control group, comprising of children who required mechanical ventilation for less than 72 hours, and the PMV group, which consisted of children who required mechanical ventilation for 72 hours or more. Risk factors were compared and analyzed between both groups.

Results: A total of 102 participants fulfilled the inclusion criteria, 90 of whom were assigned to the control group and 12 to the PMV group (11.7%). Compared with the control group, the PMV group had a higher incidence of pulmonary hypertension at a younger age (83% vs. 23%, $p = 0.012$) and 50% of them required chronic treatment for pulmonary hypertension upon home discharge. Pneumonia during ICU stay was encountered more frequently in the PMV group (33.3% vs. 2.2%, $p = 0.0042$). In addition, the PMV group had more frequent signs of low cardiac output syndrome after surgery (25% vs. 2.2%, $p = 0.019$), longer ICU stays (7 ± 0.3 days vs. 15.6 ± 2.1 days, $p = 0.0001$), needed more days of inotropes infusion (7.5 ± 0.4 days vs. 11.1 ± 1.6 days, $p = 0.0045$), and required more sedative and paralytic agents postoperatively (6 ± 0.6 days vs. 8.7 ± 1 days, $p = 0.022$).

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Conclusion: Overall, 11.7% of DS patients required prolonged ventilation after cardiac surgery. Pulmonary hypertension was seen more frequently in cases requiring PMV, and half of PMV cases required antipulmonary hypertension medication upon discharge. Early recognition of pulmonary hypertension and proper perioperative management are recommended to avoid serious complication and comorbidity after cardiac surgery.

Contents

Introduction

Down syndrome (DS) is a well-recognized genetic condition associated with several medical abnormalities especially congenital heart diseases (CHDs), which are seen in 30–50% of children with DS [1]. With progression of cardiac surgery and overall medical care, most DS patients are successfully palliated or repaired and as such, they constitute a significant population in the pediatric cardiac surgical unit. Respiratory problems are important causes of morbidity and hospital admissions among children with Down's syndrome [2]. Many factors may contribute to respiratory difficulties in DS children, including hypotonia, congenital lower airway problems, tracheobronchomalacia, and adenoid hypertrophy, which are frequently subclinical or underdiagnosed [2]. Furthermore, in children with DS, there is an increased risk of abnormalities of lung development [2]. In a *postmortem* study of children with heart diseases, six out of seven children with Down's syndrome were found to have hypoplastic lungs with a decreased number of terminal lung units and alveoli [3].

It has been recognized that the prevalence of pulmonary hypertension (PHT) in children with Down's syndrome is greater than that in children without Down's syndrome [1]. This can be explained by multiple factors such as abnormal lung vasculature growth, alveolar hypoventilation, recurrent pulmonary infections, abnormal media of pulmonary arterioles, and diminished alveoli density in addition to other nonpulmonary diseases such as gastroesophageal reflux that also contribute to the development of chronic lung disease and worsen PHT [2].

Although mechanical ventilation is lifesaving in critically ill patients, it is not without risks. Prolonged mechanical ventilation (PMV) is a well-known complication that can happen in children undergoing cardiac surgery. Many papers have described DS as one of the possible risk factors for PMV need after cardiac surgery, but investigations of the causes of PMV in the DS population is lacking [4]. Identifying the incidence and risk factors of PMV in this special group of children with CHD may help in preventing the morbidity and mortality during early postoperative and long-term care.

Definition of prolonged ventilation after pediatric cardiac surgery is a subject of debate. Some papers classified duration of mechanical ventilation to be medium duration if needed for more than 72 hours and prolonged if needed for more than 7 days [5]. Other studies considered prolonged ventilation to be the case if patients cannot be extubated within 3 days after cardiac surgery [6].

In our study, we considered mechanical ventilation prolonged if it is needed 72 hours or more after cardiac surgery. The aim of this study is to investigate the risk factors of PMV in DS children after cardiac surgery, with the goal of achieving better prevention and management of such contributing factors.

Methods

This prospective noninterventional observational study was undertaken at the Cardiac Surgical Intensive Care Unit at Prince Sultan Cardiac Center-Qassim between November 2013 and October 2016 after Institutional Research Board approval. We included all DS children with cardiac disease who underwent corrective or palliative surgery. Demographic data such as age, weight, and sex were collected. Perioperative data that include risk adjustment for congenital heart surgery (RACHS) score, cardiopulmonary bypass time, cross-clamping time, duration of mechanical ventilation in hours, evidence of PHT, use of inhaled nitric oxide, extubation failure, using of noninvasive mechanical ventilation, respiratory complication such as (pneumothorax, abnormal secretion, chylothorax, wheezes, upper airway obstruction, lung collapse), cardiac complication (signs of shock or low cardiac output, arrhythmia), evidence of infection, sedation and muscle relaxant infusion rate, and inotropic score were all collected. Gastroenterology problems such as gastroesophageal reflux disease and feeding intolerance were also documented.

We used the guidelines from the American Heart Association and American Thoracic Society for diagnosis [7] of PHT that depend on echocardiographic findings prior to and after surgery looking specifically for a tricuspid valve regurgitation gradient or a shunt direction through atrial septal defect or a degree of pulmonary regurgitation. Measurement of pulmonary artery pressure was achieved in some preoperative patients via direct measurements of the pulmonary artery pressure during cardiac catheterization or intraoperatively by the surgeon, whereas in other cases indirect estimation was done depending on oxygen saturation and the fraction of oxygen in blood gases with support of echocardiographic assessment. In our postoperative cases, none of our patients had a pulmonary artery catheter inserted so estimation of pulmonary artery pressure was estimated based on clinical and echocardiographic evaluation during postoperative intensive care unit (ICU) care. Patients were considered to develop pulmonary hypertensive crisis postoperatively if they exhibited incidents that fulfill the following criteria: sudden development of otherwise unexplained hypoxia with precipitous decrease in O_2 saturation below 70% followed by: (1) systemic hypotension with systolic blood pressure < 95th percentile for age; (2) (CVP) Central Venous Pressure > 10 mmHg ; and (3) clinical improvement with the administration of analgesia and paralysis while bagging with 100% FIO_2 (inspired oxygen fraction) with or without the use of (NOi) inhaled Nitric Oxide.

After collecting data, the cases were divided based on mechanical ventilation duration into two groups, the PMV group who had mechanical ventilation for 72 hours or more, and the control group who had less than 72 hours of mechanical ventilation. Data were analyzed and compared between two groups using GraphPad Software San Diego California.

Continuous data were analyzed between groups using unpaired Student t test. Data are presented as mean ± standard error of the mean, and $p <$ 0.05 was considered statistically significant.

Results

A total of 102 children who had complete data during the study period were included; 90 of them were assigned to the control group and 12 (11.7%) to the PMV group. Seventy-four patients had total repair of their cardiac defect, whereas 28 patients had palliative surgery, mostly pulmonary artery banding with one case in the PMV group while the others ($n = 27$) were in the control group. Mean ventilation duration in the control and PMV groups was 22 ± 1.3 hours and 150.5 ± 41.5 hours, respectively ($p = 0.0001$). Patients who required PMV were younger than their counterparts in the control group [mean age, 5.5 ± 0.8 months (PMV) vs. 12 ± 1.2 months (control group); $p =$ of 0.048; Table 1]. There were no significant differences in weight or cross-clamp time, cardiopulmonary bypass time, or RACHS score (Table 1) between the two groups. In total, 31 of 102 patients had PHT: 21/90 cases (23%) in the control group versus 10/12 cases (83%) in the PMV group ($p = 0.012$). Sixty percent of DS

Table 1. Demographic data for prolonged mechanical ventilation (PMV) and control groups.

Variable	Control group (n = 90)	PMV group (n = 12)	p
Age (mo)	12 + 1.2	5.5 + 0.8	0.048
Weight (kg)	6.9 + 0.32	5.1 + 0.4	0.28
Bypass time (min)	95.4 + 5	99.2 + 12	0.76
Cross clamping time (min)	75 + 4	82.5 + 10.3	0.45

patients with PHT required chronic PHT treatment upon home discharge, comprising 15 cases (16%) in the control group and six cases (50%) in the PMV group (Table 2). Pneumonia was encountered more frequently in the PMV group (p = 0.004, Table 2). The PMV group suffered more from signs of respiratory distress and increased work of breathing after extubation in comparison with the control group (p = 0.001, Table 2). The PMV group suffered more frequently from postoperative low cardiac output syndrome (p = 0.019) and shock (p = 0.017), stayed longer in the ICU (p = 0.0001), needed more days of inotropes infusion (p = 0.0001), had a higher inotropes score (p = 0.0045), required more sedation infusion (p = 0.003), and postoperatively needed more muscle relaxants (p = 0.022) (Tables 2 and 3).

Discussion

DS, caused by trisomy 21, is the most common chromosomal abnormality in the pediatric age group, affecting one in every 600–800 live births. Overall, 30–50% of DS patients have CHD; most of these defects require heart surgery [8]. Cardiac management is often the dominant focus of medical attention during infancy. Life expectancy for children with DS with minor or repaired cardiac defects is approximately 60 years [8].

Most studies on DS after cardiac surgery agreed that DS did not confer significant mortality risks for the common operations performed in this population [9]. These include mainly atrioventricular septal defect repair, ventricular septal defect repair, atrial septal defect repair, repair, and

Table 2. Comparison between different risk factor between two groups.

Variable	Control group (n = 90)	Prolonged ventilation group (n = 12)	p
Death	1.1% (1.1%)	1 (8.3%)	0.23
Pre surgery mechanical ventilation	8 (8.8%)	1 (8.3%)	1
Significant pulmonary hypertension	21 (23%)	10 (83%)	0.012
Extubation failure	3 (3.3%)	5 (41%)	0.001
Inhaled nitric oxide	6 (6.6%)	2 (16.6%)	0.26
Shock	0 (0%)	2 (16.6%)	0.017
Low cardiac output	2 (2.2%)	3 (25%)	0.019
Cardiopulmonary resuscitation	3 (3.3%)	1 (8.3%)	0.412
Gastroesophageal reflux	8 (8.8%)	3 (25%)	0.16
Arrhythmia	14 (15.5%)	3 (25%)	0.45
Pneumothorax	4 (4.4%)	0(0%)	1
Chylothorax	6 (6.6%)	2 (16.6%)	0.26
Previous infection	18 (20%)	3 (25%)	0.72
Pneumonia	2 (2.2%)	4 (33%)	0.0042
Hypothyroidism	29 (32%)	7 (58%)	0.26
Non-invasive ventilation	19 (21%)	7 (58%)	0.06
Secretion	39 (43%)	9 (75%)	0.3
Postoperative bronchospasm and wheezy chest	40 (44%)	9 (75%)	0.32
Upper airway obstruction	4 (4.4%)	1 (8.3%)	0.48
Work of breathing	7 (7.7%)	10 (83%)	0.001
Lung collapse	33 (36%)	7 (58%)	0.41
Sildenafil need postoperatively	15 (16.6%)	6 (50%)	0.02

Table 3. Comparison between different risk factors between the two groups.

Variable	Control group (n = 90)	Prolonged ventilation group (n = 12)	p
Intensive care stay (d)	7 ± 0.3	15.6 ± 2.1	0.0001
Ventilation duration (h)	22 ± 1.3	150.5 ± 41.5	0.0001
Inotropes score	7.5 ± 0.4	11.1 ± 1.6	0.0045
Inotropes duration (d)	2.3 ± 0.11	6 ± 1.6	0.0001
Max[*] Midazolam infusion (µg/kg/min)	0.65 ± 0.05	1.1 ± 0.22	0.003
Max Fentanyl infusion (µg/kg/h)	2.9 ± 0.14	3.4 ± 0.23	0.17
Max Morphine infusion (µg/kg/h)	5.8 ± 0.4	6.4 ± 0.96	0.5
Max Dexmedetomidine infusion (µg/kg/min)	0.42 ± 0.02	0.53 ± 0.03	0.051
Muscle relaxant infusion (µg/kg/min)	6 ± 0.6	8.7 ± 1	0.022
(NGT) nasogastric tube feeding duration (d)	3.6 ± 0.5	6.12 ± 1.6	0.061
Duration of antibiotic (d)	5 ± 0.2	10 ± 2	0.0001

Max = maximum; NGT = .
[*] P below 0.05.

patent ductus arteriosus closure [10]. Interestingly, some studies such as the one tetralogy of Fallot reported by Formigari et al. [10] declared that DS had decreased mortality rate in comparison with patients with similar cardiac defects and normal karyotype. Although it appears that DS has no obvious impact on cardiac surgical mortality, several reports identified increased incidence and risk of certain complications in this population such as arrhythmia, pacemaker need, and longer ICU stay [4,8].

In terms of the need for prolonged ventilation, there is little information about children with DS. In general, among pediatric patients, the incidence of PMV after cardiac surgery was reported to be 6% [10]. In one study, the authors described the need for more than 3 days of mechanical ventilation in 32% of postoperative cardiac children and more than 7 days in 20% of them [11].

In our study, the main respiratory problems seen in DS cases ranged from a simple manifestation such as a wheezy chest associated with a mild reactive airway disease in 48% of cases that resolved with inhaled bronchodilators in the majority of cases or required intensive bronchodilator therapy with systemic corticosteroid in a minority of cases. Other respiratory problems encountered were partial lung collapse in 39% of patients and upper airway obstruction in 5.8% of patients. Noninvasive mechanical ventilation, mainly high flow nasal cannula or continuous positive airway pressure, were used in 27.5% of patients after extubation with no difference between the control and PMV groups. By contrast, patients in the PMV group needed more days of inotropes infusion and had a higher inotropes score than those in the control group and they required more sedation and muscle relaxation, indicating that they were in general sicker than those in the control group.

PMV is a major comorbidity that a patient may face inside the ICU. DS patients have unique respiratory problems which may expose them to PMV need after cardiac surgery. These include general hypotonia, compromised upper airway by enlarged adenoid, small lower airway volume, tracheobronchomalacia, pulmonary hypoplasia, and gastroesophageal reflux disease leading to chronic aspiration [2]. Furthermore, cardiopulmonary bypass surgery can provoke pulmonary insult through propagation of inflammatory response involving cytokines, complement, neutrophils, monocytes, activated endothelial cells, and platelets that lead to pulmonary injury and may contribute to PMV support [4,12].

Several risk factors for PMV in infants and children undergoing cardiac surgery have been suggested. Doaa et al. [14] pointed out the following risk factors—RACHS (risk adjustment for congenital heart surgery)-1, low cardiac output syndrome, postoperative PHT, and postoperative arrhythmia—as potential risk factors for PMV [13]. López et al. [12] found that body weight of less than 7 kg and extrapulmonary complications are important risk factors associated with PMV after cardiac surgery in children. In the Avisa study, the incidence of PMV more than 72 hours and more than 7 days were 20% and 10.7%, respectively, and using multivariate analyses they found that younger age, lower body weight, heart failure, higher doses of inotropes, PHT, respiratory infections, and delayed sternal closure were independent predictors of PMV [5].

All previously reported studies investigated the incidence of PMV in general pediatric patients undergoing cardiac surgery, although some of them mentioned DS as one of the risk factors of PMV [14]. In our study, we looked exclusively at the underlying risk factors for PMV in DS patients after cardiac surgery and we found that 11.7% of them required more than 72 hours of mechanical ventilation. Unlike previously reported findings in cardiac children with normal karyotype, we observed that DS patients in the PMV group had no significant difference in RACHS-1 score or cardiopulmonary bypass time or cross-clamping time in comparison with the control group [15].

We observed PHT in 31 of 102 (30%) DS patients, which was higher than the previously reported incidence in nonsyndromic patients who underwent cardiac surgery [14]. Lindberg et al. [16] collected data from 1349 children younger than 18 years who had undergone cardiothoracic surgery and found that only 27 of them (2%) suffered from severe PHT. They also reported in the same study that severe PHT was more common after correction of complete atrioventricular septal defects. They likewise described that 9.9% of children with DS developed severe PHT or PHT crisis. In our study, 30% of DS patients suffered from PHT and 10/31 (32%) of those with PHT required PMV. Moreover, 20% of DS cases were discharged home on therapy for management of PHT (50% in the PMV group vs. 16% in the control group).

Brige et al. [1] studied the incidence of PHT in DS with CHD and compared them with PHT incidence in nonsyndromic patients with comparable CHD. They found that PHT was more prevalent among DS children with CHD (18/42, 42%) than in the nonsyndromic matching group (7/38, 18%;

p = 0.038). Our result was slightly different, with the incidence of PHT recorded in 30% (31/102) of DS cases. In the PMV group, 83% of cases had PHT, whereas in the control group 23% (21/90) of cases had PHT. The difference between both groups was statically significant (p = 0.012), indicating that PHT is an important risk factor for PMV need after surgery. Vazquez-Antona et al. [17] compared 16 DS patients with different types of CHD and 14 patients with matching CHD and normal karyotype, and demonstrated that DS patients with CHD had greater predisposition to develop irreversible (PAH) Pulmonary hypertension especially with (AVSD) AtrioVentricular Septal Defect [16]. There are several known causes of PHT among children with DS other than left-to-right shunt that include chronic upper airway obstruction due to midfacial hypoplasia, macroglossia, narrowing of nasopharynx, adenoid hypertrophy, and laryngotracheomalacia [2]. In addition, they may have frequent obstructive sleep apnea, recurrent chest infection, abnormal pulmonary vasculature, and alveolar hypoventilation [2]. Furthermore, there is some evidence that infants with DS have some degree of pulmonary hypoplasia [3]. In their study, Cooney and Thurlbeck [3] looked at the lung architecture in seven children with DS and found poor development of respiratory architecture in six of them. Weijerman et al. [18] assessed the prevalence of congenital heart defects and persistent PHT in neonates with DS and found higher incidence of PHT (5.2%) compared with the general population (p < 0.001).

Interestingly, our data showed that all DS patient who needed PMV were younger than those in the control group, which supports the idea that PHT in DS patients started earlier prior to the time that is usually expected for CHD to contribute to increase pulmonary pressure in non-syndromic children who have similar CHD. This may support the idea that there are multiple factors in DS that predispose these children to early PHT development in the presence of CHD.

Proper investigations and early recognition and treatment of the other causes for PHT, especially enlarged adenoid leading to sleep apnea and gastroesophageal reflux diseases leading to aspiration, may help to avoid exacerbation of PHT associated with CHD. Educating the parents on this topic and assembling a multidisciplinary team that includes a pulmonologist, a gastroenterologist, a respiratory therapist, and a social worker may help in the management of DS cases and ensure a comprehensive approach to manage PHT prior to cardiac repair for optimal results, and after cardiac surgery for enhanced pulmonary rehabilitation.

Our study has many limitations, including the fact that this is a single-center experience with a small number of cases comprising the PMV group. We limited our findings to univariate analysis and we did not find specific risk factors by multivariate analysis. More and larger multicenter studies are needed to investigate the role of PHT in the duration of mechanical ventilation in DS patients undergoing cardiac surgery. It is possible that other contributing factors are also present that need to be addressed with larger group of patients.

Conclusion

In DS children undergoing cardiac surgery, almost 11% will require prolong positive pressure ventilation. PHT was seen more in cases requiring PMV after surgery, and many of them required extended PHT management upon discharge. Recognition and early management of causes that contribute to PHT in DS children through a multi-disciplinary approach may help in shortening the period of mechanical ventilation after cardiac repair.

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