

Extubation failure after Norwood procedure in hypoplastic left heart syndrome patients

Extubación fallida postoperación de Norwood en pacientes con síndrome de hipoplasia de ventrículo izquierdo

Adolfo Herrera J.^a, Daniel Springmüller P.^b, Paulina del Pozo B.^c,
Jaime Cerda L.^d, Rodrigo Adasme J.^e, Andrés Castillo M.^e

^aFellow of Pediatrics. Department of Pediatrics, Pontificia Universidad Católica de Chile. Santiago, Chile.

^bDepartment of Pediatric Cardiology and Pediatric Respiratory Disease, Division of Pediatrics, Pontificia Universidad Católica de Chile. Santiago, Chile.

^cPediatric Critical Care Academic Unit. Department and Division of Pediatrics, Pontificia Universidad Católica de Chile. Santiago, Chile.

^dDepartment of Public Health, Pontificia Universidad Católica de Chile. Santiago, Chile.

^eEpidemiology Master, Certified Respiratory Therapist. Respiratory Care Team. Hospital Clínico Red de Salud UC-Christus. Escuela de Kinesiología. Facultad de Ciencias de la Rehabilitación. Universidad Andrés Bello, Chile.

Received: 15-4-2019; Approved: 13-4-2020

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

Hypoplastic left heart syndrome (HLHS) is the main cause of neonatal mortality due to congenital heart disease. Recent reports have described that, after Norwood surgery, patients with extubation failure present higher mortality than those without.

What does this study contribute to what is already known?

There are few studies in the literature evaluating extubation failure and associated risk factors in this group of patients. Although extubation failure was not associated with an increased mortality in our patients, we were able to identify risk factors that could be modified.

Abstract

Hypoplastic left heart syndrome (HLHS) is the main cause of mortality due to congenital heart disease. The Norwood surgery is the first procedure of the surgical staging process towards a single ventricle physiology or Fontan-type operation and has a mortality rate of 10% to 30%. Extubation failure during the postoperative period occurs in up to 18% of these patients and is associated with increased mortality. **Objective:** To describe extubation failure rates and risk factors in pediatric patients with HLHS who underwent Norwood procedure. **Patients and Method:** Case-control study that included all the patients with HLHS managed with Norwood surgery at the Hospital Clínico de la Pontificia Universidad Católica between January 2000 and February 2018. Cases and controls were defined as patients with extubation failure and as patients without this complication, respectively. The fo-

Keywords:

Hypoplastic left heart syndrome;
Norwood procedure;
airway extubation;
congenital heart disease

Correspondence:
Andrés Castillo M.
acastill@med.puc.cl

llowing variables were recorded demographic, surgical, and post-surgical ones, and univariate and multivariate analyses (logistic regression) were performed to determine risk factors associated with extubation failure. **Results:** Out of 107 patients, 26 of them presented extubation failure (24.3%). In the univariate analysis, longer mechanical ventilation time during the postsurgical period, atelectasis, pleural effusion, chylothorax, other respiratory morbidities (i.e. apneas and tracheitis), and longer infusion times of morphine and midazolam, all were associated with a higher extubation failure rate in this population. In the multivariable analysis, chylothorax, other respiratory comorbidities, and longer infusion time of midazolam remained associated with this complication, however, it was not associated with higher mortality. **Conclusions:** Chylothorax, respiratory comorbidities, and longer use of Midazolam should be addressed before planning airway extubation in order to avoid failure.

Introduction

Hypoplastic left heart syndrome (HLHS) is a spectrum of congenital heart malformations characterized by different degrees of left ventricle and aortic arch hypoplasia, accounting for up to 7.5% of all congenital heart diseases. It is currently the leading cause of neonatal mortality due to congenital heart disease, with a 95% mortality rate at one month of age without treatment^{1,2}.

Currently, the most common surgical option is a 3-stage palliation, known as the Norwood, Glenn or Fontan surgeries. Patients who undergo this surgical sequence have a 5-year survival rate of 57%. Mortality is mainly related to the first surgery, the Norwood procedure, ranging from 10 to 30%, as reported in the literature^{3,4}.

In 2000, the Hospital Clínico de la Pontificia Universidad Católica de Chile was the first national health center that started a heart surgery program for HLHS using the Norwood procedure and is currently one of the three main centers providing health services to the Public Health System in Chile for this type of pathology. In our center, the reported post-operative mortality has decreased in recent years, with 36% between 2000 and 2005, and 15% between 2005 and 2010⁴.

In adult Intensive Care Unit (ICU) patients, a statistically significant association between extubation failure and postoperative mortality has been reported with an OR of 7.3 (95% CI 4.6-11.7)⁵. In a recent series of pediatric patients, it was found that after the Norwood operation, patients with extubation failure have up to 5 times more mortality than those without⁶.

Recent reports carried out in our center showed an extubation failure frequency of 18% in 76 patients after the Norwood operation⁴, twice more frequent as that observed in patients undergoing surgeries due to other congenital heart diseases⁷. The high incidence of extubation failure in this group of patients and its associated high mortality make extubation failure an important factor in the evaluation of the quality of post-surgical management of these patients.

Few studies in the literature directly analyze extubation failure and associated risk factors in this group of patients⁸. In addition, we do not know how our national reality has changed regarding this complication and if there is any modifiable risk factor that could reduce the extubation failure rate and improve the survival of these patients.

Based on the above, the objective of this study is to describe the extubation failure rate and the factors that are associated with this complication in pediatric HLHS patients managed with Norwood procedure.

Patients and Method

Observational, retrospective, case-control study. We included all patients diagnosed with HLHS who received surgical treatment with either a Norwood-Sano shunt (RV-PA conduit) or Norwood-Modified Blalock-Taussig shunt (mBTS), and subsequently hospitalized in the Pediatric Critical Care Unit of the Hospital Clínico de la Pontificia Universidad Católica de Chile between January 2000 and February 2018. We excluded patients with HLHS who did not undergo a Norwood-Sano or Norwood-BTS operations (i.e. Hybrid Stage 1 surgery) and those who died during their perioperative period immediately before extubation.

Pre- and post-operative follow-up was performed, up to 72 hours after extubation. Patients with successful extubation were classified as controls, and patients with extubation failure as cases. Extubation failure was defined as the need for reintubation in the first 48 hours after extubation. Mortality was considered within the postoperative period until discharge or transfer to another center.

General and demographic data on the included patients, their baseline cardiac anatomy, surgical procedure, ventilatory and cardiovascular management, postoperative complications, and medication use were collected from the medical records by a single reviewer. The IBM SPSS Statistics v. 21.0 software was used for the statistical analysis. A univariate analysis was performed using the Chi-square test for categorical va-

riables and the Student T-test and Wilcoxon test for continuous ones. A multivariate analysis was also performed using logistic regression that included all the statistically significant results obtained from the univariate analysis.

This study was approved by the Ethics Committee of the Medicine School of the Pontificia Universidad Católica de Chile.

Results

During the studied period, 128 patients with HLHS underwent the Norwood procedure, 21 were excluded because they did not meet the inclusion criteria (7 did not correspond to Norwood-Sano or Norwood-BTS operations and 14 died before being extubated). Out of the 107 patients analyzed, 26 (24.3%) presented extubation failure after the Norwood operation, and out of these, 20 presented extubation failure in the first 24 hours after extubation, while the remaining patients did it in the following 24 hours. The median time from extubation to extubation failure was 15 hours (interquartile range of 7-23 hours).

When analyzing the demographic and surgical variables, there were no statistically significant differences between the two groups (Table 1). In relation to the presence of genopathies in the studied patients, there were 5 patients on the extubation failure group: 3 with

a suspected genetic syndrome, 1 with Turner syndrome, 1 with Ellis Van Creveld syndrome and 1 with Triple X syndrome, compared to 5 patients in the group without extubation failure: 2 patients with Heterotaxy Syndrome, 1 with DiGeorge Syndrome, 1 with duplication of the short arm of chromosome 8, and 1 with suspected genetic syndrome.

Regarding ventilatory management, the extubation failure group presented significantly longer post-surgical mechanical ventilation time (200 ± 84 hours versus 148 ± 57 hours; $p < 0.01$), shorter use of non-invasive mechanical ventilation (NIMV) after extubation (8 ± 7 hours versus 38 ± 23 hours; $p < 0.01$), shorter use of high-flow nasal cannula (HFNC) after extubation (2 ± 0.5 hour versus 40 ± 27 hour; $p < 0.01$), with a higher NIMV use rate (52% versus 18.7%; $p < 0.01$). None of the patients underwent a specific test protocol for spontaneous ventilation, initiation of NIMV, or use of HFNC, which was at the discretion of the attending physician. Concerning the other variables analyzed in ventilatory management, no statistically significant differences were found between the two groups (Table 2).

In relation to postoperative complications and the use of medications before extubation, the extubation failure group presented statistically significant higher rates of atelectasis (36% vs. 14.8%), pleural effusion (32% vs. 8.6%), and chylothorax (32% vs. 6.2%). Also, 23.1%

Table 1. Clinical and Surgical Variables between patients with and without extubation failure after Norwood procedure

Patient factors	Extubation failure (n = 26)	Extubation Success (n = 81)	p-value
Male: number (%)	12 (46.2%)	48 (59.3%)	0.26
Gestational age: weeks ($\pm$ SD)	38 ($\pm$ 1.27)	38 ($\pm$ 1.09)	0.66
Birth weight: grams ($\pm$ SD)	3134 ($\pm$ 394)	3257 ($\pm$ 458)	0.22
Genetic syndrome: number (%)	5 (19.2%)	5 (6.2%)	0.06
Airway abnormalities: number (%)	0 (0%)	3 (3.7%)	1
Ascending aorta diameter: mm ($\pm$ SD)	3.5 ($\pm$ 1.6)	3.3 ($\pm$ 1.5)	0.6
Norwood-Sano vs. Norwood BTS: number (%)	22 (84.6%)	75 (92.6%)	0.25
Age at surgery: days ($\pm$ SD)	10 ($\pm$ 5)	11 ($\pm$ 8)	0.51
Weight at surgery: grams ($\pm$ SD)	3241 ($\pm$ 370)	3374 ($\pm$ 459)	0.18
Total surgical time: min ($\pm$ SD)	397 ($\pm$ 82)	396 ($\pm$ 72)	0.95
Cardiopulmonary bypass time: min ($\pm$ SD)	206 ($\pm$ 43)	209 ($\pm$ 29)	0.69
Cross clamp time ($\pm$ SD)	84 ($\pm$ 27)	92 ($\pm$ 25)	0.17
RCP time: min ($\pm$ SD)	70 ($\pm$ 19)	76 ($\pm$ 18)	0.18
DHCA time: min ($\pm$ SD)	20 ($\pm$ 12)	16 ($\pm$ 6)	0.06
Modified ultrafiltration: mL ($\pm$ SD)	370 ($\pm$ 201)	342 ($\pm$ 152)	0.61

BTS = Blalock-Taussig shunt; CPB = cardiopulmonary bypass; RCP = regional cerebral perfusion; DHCA = Deep Hypothermia and Circulatory Arrest.

Table 2. Ventilation variables between patients with and without extubation failure after Norwood procedure

Patient factors	Extubation failure (n = 26)	Extubation Success (n = 81)	p-value
Intubation before surgery: number (%)	18 (75%)	54 (78.3%)	0.78
Cuffed endotracheal tube: number (%)	6 (26.1%)	21 (35%)	0.60
Time in IMV: hours ($\pm$ SD)	304 ($\pm$ 156)	262 ($\pm$ 121)	0.19
Post-op IMV: hours ($\pm$ SD)	200 ($\pm$ 84)	148 ($\pm$ 57)	< 0.01
iNO use: number (%)	3 (12.5%)	5 (7.6%)	0.43
Time of iNO use: hours ($\pm$ SD)	150 ($\pm$ 76)	114 ($\pm$ 61)	0.85
NIMV use post extubation: number (%)	13 (52%)	14 (18.7%)	< 0.01
Time in NIMV post extubation: hours ($\pm$ SD)	8 ($\pm$ 7)	38 ($\pm$ 23)	< 0.01
HFNC use post extubation: number (%)	4 (16%)	10 (13.3%)	0.74
Time in HFNC post extubation: hours ($\pm$ SD)	2 ($\pm$ 0.5)	40 ($\pm$ 27)	< 0.01

IMV = invasive mechanical ventilation; iNO = inhaled nitric oxide; NIMV= non invasive mechanical ventilation; HFNC = high flow nasal cannula.

of patients with extubation failure presented other respiratory complications (apneas, tracheitis, pneumonia, and pulmonary hemorrhage). Significant differences were also found in the length of morphine infusion before extubation (88 ± 55 hours versus 64 ± 44 hours;

$p = 0.04$) and length of midazolam infusion (152 ± 60 hours versus 109 ± 44 hours; $p < 0.01$). Finally, mortality after extubation was 2 of 26 patients (7.7%) in the extubation failure group versus 9 of 81 patients (11.1%) in the non-failure group ($p = 0.62$) (Table 3).

Table 3. Post-operative complications and medications use between patients with and without extubation failure after Norwood procedure

Patient factors	Extubation failure (n = 26)	Extubation Success (n = 81)	p-value
Diaphragm paralysis: number (%)	0 (0%)	1 (1.2%)	1
Vocal cord paralysis: number (%)	8 (32%)	21 (25.9%)	0.61
Atelectasis: number (%)	9 (36%)	12 (14.8)	0.04
Pneumothorax: number (%)	1 (4%)	2 (2.5%)	0.55
Consolidation: number (%)	3 (12%)	3 (3.7%)	0.14
Pleural effusion: number (%)	8 (32%)	7 (8.6%)	< 0.01
Chylothorax: number (%)	8 (32%)	5 (6.2%)	< 0.01
Cardiovascular complications: number (%)	6 (23.1%)	6 (7.4%)	0.45
Other respiratory complications: number (%)	6 (23.1%)	5 (6.2%)	0.02
Metabolic complications: number (%)	3 (11.5%)	14 (17.3%)	0.75
Infectious disease comorbidities: number (%)	11 (42.3%)	27 (33.3%)	0.48
Neurological complications: number (%)	5 (19.2%)	7 (8.6%)	0.16
Fentanyl postoperative time of use (hours) ($\pm$ SD)	69 ($\pm$ 25)	56 ($\pm$ 26)	0.06
Morphine postoperative time of use (hours) ($\pm$ SD)	88 ($\pm$ 50)	64 ($\pm$ 44)	0.04
Midazolam postoperative time of use (hours) ($\pm$ SD)	152 ($\pm$ 60)	109 ($\pm$ 44)	< 0.01
Use of antiarrhythmics: number (%)	1 (4.3%)	3 (4.5%)	1
Postextubation Inotrope score: number ($\pm$ SD)	3 ($\pm$ 3)	4 ($\pm$ 3)	0.6
Vasoactive Inotrope Score: number ($\pm$ SD)	7 ($\pm$ 3)	8 ($\pm$ 3)	0.1
Preextubation corticosteroids: number (%)	1 (4.2%)	0 (0%)	0.28
Death: number (%)	2 (7.7%)	9 (11.1%)	0.65

Other respiratory complications: apnea, tracheitis, pneumonia and pulmonary hemorrhage.

Table 4. Statistically significant variables after a multivariate analysis

Variable	p-value	OR	95% confidence interval
Chylothorax	0.01	1.83	1.33-1.95
Other respiratory comorbidities:	0.02	1.8	1.20-1.95
Midazolam postoperative time of use (hours)	0.01	1.01	1.00-1.03

Other respiratory comorbidities: apnea, tracheitis, pneumonia and pulmonary hemorrhage.

With respect to cardiovascular postoperative complications, 6 complications were observed in the extubation failure group (3 arrhythmias, 1 intra-auricular thrombosis, 1 coronary embolism, and 1 aortic stenosis), and 6 in the non-extubation failure group (2 arrhythmias, 1 intra-auricular thrombosis, 2 cardiac tamponade, and 1 postoperative bleeding). However, when analyzing the relationship between these complications and extubation failure rate, there was no significant difference (Table 3).

In the multivariate analysis, including all statistically significant variables obtained from univariate analysis, 3 variables remained with a statistically significant difference after adjustment: presence of chylothorax (OR: 1.83; 95% CI 1.33-1.95), other respiratory complications (OR: 1.8; 95% CI 1.2-1.95) and duration of post-operative midazolam use (OR: 1.01; 95% CI 1.00-1.03) (Table 4).

Discussion

In this study, we observed that patients with HLHS undergoing a Norwood-Sano or Norwood-BTS operation had a 24.3% rate of extubation failure in the postoperative period. This rate is higher than the 18.4% described by Urcelay et al. in 2016, in a descriptive review of outcomes in patients with HLHS operated between years 2000 and 2012 at our institution⁴. However, it is similar to the rate described by Gupta et al. in 2012, who described a 22% of extubation failure after Norwood surgery in 64 patients⁸. These rates are higher than those described in our center after surgical correction of all congenital heart disease, which reaches 9%⁷. This highlights the degree of management complexity of patients with HLHS when compared with other cardiac malformations.

The variables that showed significant association with extubation failure in the univariate analysis are mainly related to perioperative management and respiratory complications, as well as the use of opioid and benzodiazepine infusions that may affect respiratory function. We highlight the association of extubation failure with duration of invasive mechanical venti-

lation, the presence of atelectasis, pleural effusion or chylothorax, and hours of morphine and midazolam use before extubation. In the multivariate analysis, the presence of chylothorax and other respiratory comorbidities stands out, both with an OR of 1.8. The association with the duration of midazolam use (OR: 1.01; 95% CI; 1.00-1.03) should be mentioned since it is a modifiable risk factor. The presence or suspicion of a genetic syndrome was associated with a higher rate of extubation failure, without statistical significance in this group of patients ($p = 0.06$).

Regarding the use of NIMV, despite the extubation failure group presented a higher percentage of its use than the successful extubation group, this is not a risk factor, but a variable without causal association. This can be explained because the use of NIMV in our Unit is a preventive or rescue measure in cases of imminent extubation failure that aims to avoid reintubation in patients with poor cardio-respiratory performance. The short duration of NIMV use in the patients of the extubation failure group could be explained because our ICU medical team continuously assess these patients in order to avoid prolonging its use in those patients with evident respiratory failure. Therefore, the high percentage of NIMV use and the low number of hours used in these patients do not represent a risk factor. Although the use of non-invasive methods before reintubation may be important, there is currently no protocol in our unit for the use of NIMV or HFNC in these patients, which could directly influence the rate of reintubation. Moreover, the results of this study will allow us the elaboration of a clear and objective protocol for the use of these resources, so that their use is not at the complete discretion of the attending physician.

Similar to the experience reported by Gupta et al.⁸, we can see that there were significant differences in the time of use post-surgical invasive mechanical ventilation and presence of atelectasis or pneumonia (included in the 'other respiratory complications' variable of this article). But in our series, we did not show any relationship between extubation failure and airway malformations, diaphragmatic paralysis, nitric oxide use, type of surgical procedure (Norwood-Sano and

Norwood-BTS) or inotropic score after surgery. The low frequency of some of these conditions may have played a role in this lack of association. Other variables, which in this series showed no association with extubation failure, are sex, gestational age, birth weight, ascending aortic diameter, age and weight at the time of surgery, weight at extubation, and difference in weight between surgery and extubation. The mean surgical duration, amount of modified ultrafiltration, infectious, neurological, and metabolic comorbidities, use of antiarrhythmics, inotropic, and vasoactive- inotropic score at different post-surgical times were also not associated with extubation failure.

Regarding mortality in this group of patients, Scodellaro et al.⁶ reported an increase in mortality in up to 5 times in patients with extubation failure versus those without it. The 7.7% mortality rate observed in this study after extubation failure is similar to that reported by Gupta et al.⁸. However, in our study, extubation failure did not represent a risk factor for postoperative mortality. This lack of association may be due to improved medical and surgical management of these patients, as noted by Urcelay et al. in 2016⁴. However, mortality in this series only refers to patients who were successfully extubated. If we include patients who died before being extubated (14 patients excluded in our current analysis), our mortality rate was 18.2% (18 out of 99 patients), similar to that reported in 2016 by Urcelay et al.⁴.

Based on the findings of this study, and considering the multiple factors that contribute to extubation failure, we infer that patients with HLHS after Norwood procedure have labile cardiovascular physiology in which the respiratory complications (i.e. atelectasis, pulmonary hemorrhages, pneumonia, pleural effusion, or chylothorax) worsen the respiratory function, resulting in longer times of invasive mechanical ventilation and sedative drug, which eventually deteriorate cardiopulmonary function even more and, therefore, this group of patients have a higher rate of extubation failure. Thus, the presence of these complications must be properly recognized and treated in advance before considering extubation.

It is also important to recognize the limitations of this study given its retrospective nature, having a selected group of patients (only those undergoing surgery) and the lack of clear protocols in our unit for spontaneous ventilation testing before extubation or protocols for the use of non-invasive ventilatory support after extubation. Recognizing these limitations will allow us to elaborate management protocols in the future

and subsequently evaluate the influence of these in the rate of extubation failure.

The main strength of this paper is to contribute to understand how complex cardiopulmonary interactions lead to extubation failure in patients with HLHS after the Norwood operation. Despite recognizing the limitations of a retrospective review, this study adds to the knowledge of modifiable risk factors that may reduce the rate of extubation failure and thus reduce morbidity and mortality of patients with HLHS undergoing Norwood procedure.

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: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Acknowledgments

The first author of this study expresses his gratitude to the people who made it possible, to the Pediatric Intensive Care Unit of the Hospital Clínico Pontificia Universidad Católica, to the Pediatric Cardiology and Cardiosurgery Team and the people who work with the medical records.

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