Extracorporeal Membrane Oxygenation in Pediatric Trisomy 21: 30 Years of Experience from the Extracorporeal Life Support Organization Registry

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Objectives To describe the use of extracorporeal membrane oxygenation (ECMO) in patients with trisomy 21 (T21), to identify risk factors for hospital mortality, and to compare outcomes with those of patients without T21.

Study design Children under age 18 years registered in the Extracorporeal Life Support Organization Registry were included. Comparisons between patients with T21 and patients without T21 were performed using the χ^2 or Wilcoxon rank-sum test and multivariable logistic regression.

Results The study cohort included 623 patients with T21 and 46 239 patients without T21. The prevalence of T21 was 13.5/1000 patients receiving ECMO. ECMO utilization in patients with T21 increased over time, with 60% of cases occurring in the last decade. There was no significant difference in survival between patients without T21 and those with T21 (63% vs 57%; $P = .23$). In patients with T21, independent risk factors for mortality before cannulation were a cardiac indication for ECMO support and milrinone use ($P \leq .001$ for both). Multivariable risk factors for mortality on ECMO included hemorrhagic, neurologic, renal, and pulmonary complications ($P < .04$ for all).

Conclusion The use of ECMO in patients with T21 has increased over time. Patients with a cardiac indication for ECMO have higher mortality compared with those supported for respiratory indications. Despite differences in indications for ECMO, patients with T21 have similar hospital survival as those without T21; thus, by itself, a diagnosis of T21 should not be considered a risk factor for in-hospital mortality when contemplating ECMO cannulation. *(J Pediatr 2015;167:403-8)*.

Trisomy 21 (T21, also known as Down syndrome) is the most common chromosomal congenital anomaly, affecting approximately 5500 infants annually in the US alone.[1-3] T21 is characterized by delayed psychomotor development and increased risk of congenital heart disease (CHD), gastrointestinal defects, celiac disease, and hypothyroidism.[4] Children with T21 also are at greater risk of developing respiratory disease and pulmonary arterial hypertension compared with children without T21.[5,6]

Extracorporeal membrane oxygenation (ECMO) is a widely used form of mechanical circulatory support for infants and children with refractory respiratory and cardiac failure.[7] In a multicenter study that included patients from 1984-1999, neonates with T21 were found to be at significantly greater risk of undergoing ECMO for respiratory failure and had much higher post-ECMO hospital mortality than neonates without T21.[8] However, in a single-center study that included patients from the 1980s, Klein et al[9] found no difference in survival to hospital discharge between infants with T21 and those without T21 placed on ECMO after corrective heart surgery. In another single-center study, mortality was similar in children with and without genetic syndromes placed on ECMO for cardiac indications.[10] A recent multicenter study of pediatric patients with T21 reported improved outcomes after cardiac surgery in those receiving ECMO (n = 121) compared with those without ECMO.[11] That study used the Extracorporeal Life Support Organization (ELSO) database from 1998-2011 and included both neonates and children with 5 different cardiac diagnoses. Although informative, the study was limited by the restricted study period, inclusion of only selected cardiac diagnoses, and small sample size.

The primary aims of the present study were to describe ECMO use in neonates and children with T21 and to identify risk factors for hospital mortality. In addition, we sought to compare outcomes in children with T21 and those without T21 who received ECMO.

CHD	Congenital heart disease
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
PPHN	Persistent pulmonary hypertension of the newborn
T21	Trisomy 21
VA	Venoarterial
VV	Venovenous

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Methods

Study data were extracted from the ELSO Registry. The ELSO Registry became an official organization in 1989, but data collection began in 1983. The ELSO Registry currently collects case data from 244 ECMO centers worldwide through voluntary reporting on a standardized data capture form. Data include patient demographics, the primary indication for ECMO therapy (designated as "pulmonary" or "cardiac," or "extracorporeal cardiopulmonary resuscitation"), primary and secondary diagnoses, pre-ECMO physiological data, ECMO support data, complications, and vital status at hospital discharge.

The ELSO Registry was queried for all neonates (age ≤30 days) and children (age 31 days to 18 years) treated with ECMO from 1983 through July 2013 with the diagnosis of T21. For patients undergoing ECMO more than once, only data from the first run were analyzed. Outcomes of pediatric patients with T21 (entire cohort) and those without T21 were compared using the ELSO Registry data from the same time period. This study used only deidentified data and was compliant with the exempt categories of research as defined by the Institutional Review Board at Ann & Robert H. Lurie Children's Hospital of Chicago.

Statistical Analyses

Data are reported as frequency (n) with proportion (%) or as median with IQR. The primary outcome of interest was death before hospital discharge. To identify risk factors for death, univariate analyses were performed using the χ^2 or Wilcoxon rank-sum test. Variables that were associated with death in univariate analysis (ie, $P < .05$) were included in multivariable logistic regression models using a backwards stepwise selection process. Separate analyses were performed for known exposure variables present before ECMO cannulation and for exposure variables developing after ECMO. In secondary analyses, we sought to identify risk factors for mortality after creating 2 study patient subgroups based on patient age: neonates (age ≤30 days) and older children (age 31 days to 18 years). In the ELSO Registry, the mode of ECMO is recorded as venoarterial (VA), venovenous (VV), VV double lumen, VA plus additional venous cannula, VV converted to VA, or VV double lumen plus additional venous cannula. For this study, any VA ECMO (ie, VA, VA plus additional venous cannula, or VV converted to VA) was categorized as VA. Variables with missing data were included in multivariable models only if <10% of values were missing. A P value <.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

A total of 623 pediatric patients with T21 supported with ECMO had data entered into the ELSO Registry between 1983 and 2013. These included 267 neonates (aged ≤30 days) and 356 children (age 31 days to 18 years). A total of 46 916 pediatric patients (32 656 neonates and 14 260 children) supported with ECMO in 244 centers were entered in the registry during the study period. The prevalence of T21 was 13.5 per 1000 patients receiving ECMO in the ELSO Registry. The prevalence of T21 in the general population is 0.83-1.00 per 1000 live births.[1-3] Thus, patients with T21 appear to have increased prevalence in the population receiving ECMO.

ECMO use in patients with T21 has increased over time, with 60% of the cases occurring in the last of the 3 decades included in this study. Similar to recent trends of ECMO use in patients without T21, cardiac ECMO and extracorporeal cardiopulmonary resuscitation cases represent a growing proportion of patients with T21. The total number of cardiac cases has increased in each era, with only 16 cases in era 1 and 180 cases in era 3.

Risk Factors for Hospital Mortality in Pediatric Patients with T21 Known before ECMO Cannulation

The demographic data and pre-ECMO characteristics of hospital survivors and nonsurvivors are shown in Table I. In univariate analyses, age 31 days to 18 years, a diagnosis of CHD, VA ECMO, cardiac ECMO, milrinone use, and high-frequency ventilation were all associated with increased mortality, whereas the use of nitric oxide before ECMO cannulation was associated with decreased mortality (37% vs 50% mortality; $P = .001$). There were no significant differences between survivors and nonsurvivors in terms of sex, weight, or ethnicity. Interestingly, there was no significant difference in overall mortality by era (30% for 1983-1992 vs 47% for 1993-2002 vs 43% for 2003-2013; $P = .11$). With multivariate analysis, independent risk factors for mortality known before cannulation (n = 599) were cardiac ECMO (aOR, 2.2; 95% CI, 1.6-3.1) and milrinone use (aOR, 1.9; 95% CI, 1.2-3.1).

Risk Factors for Hospital Mortality in Pediatric Patients with T21 Known after ECMO Cannulation

Separate analyses were conducted to identify risk factors for mortality that developed after ECMO cannulation. Features of ECMO and complications developing after ECMO in survivors and nonsurvivors are shown in Table II. Univariate risk factors for mortality were ECMO duration >7 days and hemorrhagic, neurologic, renal, pulmonary, mechanical, cardiovascular, and metabolic complications. Multivariate risk factors for mortality on ECMO were hemorrhagic (aOR, 1.5; 95% CI, 1.1-2.3), neurologic (aOR, 2.4; 95% CI, 1.4-4.1), renal (aOR, 3.0; 95% CI, 2.0-4.5), and pulmonary (aOR, 2.3; 95% CI, 2.0-4.5) complications. Of note, mortality was higher in the 14 patients with T21 who underwent 2 ECMO runs compared with the 609 patients with T21 who underwent 1 ECMO run (71% vs 43%; $P = .04$).