Extracorporeal membrane oxygenation for respiratory failure in children: the years before and after the 2009 H1N1 pandemic

Original Article

INTRODUCTION

Respiratory failure is a frequent cause of admission to the pediatric intensive care unit (PICU). In children, the mortality rates for respiratory failure related to viral or bacterial pneumonia, trauma, and acute respiratory distress syndrome (ARDS) are still unacceptably high. Severe viral lower respiratory tract infections, including influenza, can progress to acute respiratory distress syndrome by means of acute respiratory failure, which has prompted the development of extracorporeal membrane oxygenation (ECMO) as a life-saving treatment option. ECMO is an artificial lung support technique that uses a pump to circulate the patient’s blood through an oxygenator, allowing for the removal of carbon dioxide and the provision of oxygen to the patient’s tissues. This technique has been used to support patients with respiratory failure in the setting of severe viral infections, including the first outbreak of the H1N1 influenza virus in 2009.

OBJECTIVE: To evaluate whether there was any impact on the number of pediatric extracorporeal membrane oxygenation runs and survival rates in the years subsequent to the 2009 H1N1 pandemic.

METHODS: We studied two different periods of extracorporeal membrane oxygenation support for respiratory failure in children by analyzing datasets from the Extracorporeal Life Support Organization. Autoregressive integrated moving average models were constructed to estimate the effect of the pandemic. The year 2009 was the year of intervention (the H1N1 epidemic) in an interrupted time series model. Data collected from 2001 - 2010 were considered preintervention, and data collected from 2010 - 2017 were considered postintervention.

RESULTS: There was an increase in survival rates in the period 2010 - 2017 compared to 2001 - 2010 (p < 0.0001), with a significant improvement in survival when extracorporeal membrane oxygenation was performed for acute respiratory failure due to viral pneumonia.

CONCLUSION: In the years following 2009, there was a significant, global incremental increase in the extracorporeal membrane oxygenation survival rates for all runs, mainly due to improvements in the technology and treatment protocols for acute respiratory failure related to viral pneumonia and other respiratory conditions.

KEYWORDS: Respiratory insufficiency; Extracorporeal membrane oxygenation; H1N1; Influenza A virus, H1N1 subtype; Influenza, human; Respiratory distress syndrome; ARDS; Pandemics; Survival rate; Child
of host and viral mechanisms, which include epithelial cell death, alveolar compromise, local and systemic cytokine production, innate immune cellular infiltration, exuberant T cell responses, and other innate and adaptive immune responses.\(^{(1)}\)

Acute respiratory distress syndrome is routinely managed using lung protective ventilator strategies, but if these ventilation strategies cannot provide adequate oxygenation, patients may require extracorporeal membrane oxygenation (ECMO), which has increasingly been gaining importance as a salvage therapy.\(^{(2,3)}\) The main indications for ECMO are acute severe heart or lung failure with high risk for mortality despite optimal conventional therapy. Thus, ECMO is considered when a 50% mortality risk is predicted.\(^{(4)}\)

In recent decades, health systems worldwide have been confronting new epidemic and pandemic infections. During the 2009 H1N1 pandemic, hundreds of patients with ARDS worldwide received ECMO.\(^{(5)}\) The proportion of ECMO use for influenza-associated disease has increased over time, with a peak in 2009. The overall survival rate (all ages, all centers around the world) for ECMO during the 2009 pandemic was 60%, as reported by de St Maurice et al. in a study that explored the International Extracorporeal Life Support Organization (ELSO) database.\(^{(6)}\) The ELSO is an organization intended to assist institutions in delivering extracorporeal life support through education, guideline development, original research, publications, and maintenance of a comprehensive registry that, in 2020, included data on more than 130,000 patients.\(^{(7)}\)

As the applications of ECMO in children grow, the analysis of outcomes is becoming increasingly important to ensure that this therapy remains available for appropriate candidates and to ensure better long-term survival and functional prognosis.\(^{(8)}\)

This study evaluated, in a historical series, whether in the years subsequent to the 2009 pandemic there has been any impact on the number of pediatric ECMO runs and survival rates.

**METHODS**

We analyzed the summary datasets from the ECMO Registry of Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI, https://www.elso.org/).

Data from patients aged 1 month to 18 years were included and used to calculate the ECMO usage and survival (to hospital discharge) rates. The frequencies were analyzed using chi-square and Fisher’s exact tests, with 95% confidence intervals (95% CIs) and a significance level of 0.05. We built a time series using the data available for the total number of pediatric respiratory runs with the interrupted time series method, whose characteristics are the data collected at multiple points before and after an intervention.\(^{(9)}\) We used 2009 as the year of “intervention” (the H1N1 pandemic). Data collected from 2001 - 2010 were considered “preintervention”; 2009 data were received by ELSO and compiled until July 2010 (the “intervention” year); and data collected from July 2010 - 2017 were considered “postintervention”. Autoregressive integrated moving average (ARIMA) models were constructed, and trends and autocorrelation were considered to estimate the effect of the pandemic using Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corp. Armonk, NY).

**RESULTS**

The ECMO runs in the preintervention and postintervention periods are displayed in table 1, where we can observe increased survival rates for all runs in the second period (2010 - 2017) compared with the period (between 2001 and 2010) \((p < 0.0001)\). Table 1 also shows the ECMO runs by diseases and conditions. We observed a significant improvement in the survival rates when ECMO was performed for acute respiratory failure due to viral pneumonia and in other respiratory conditions. However, there was no improvement in survival for other forms of acute respiratory failure secondary to lung disease (non-ARDS diagnosis, aspiration pneumonia and bacterial pneumonia), ARDS in patients who required surgery after trauma, and ARDS unrelated to surgery. In the ARIMA model (Table 2), the preslope coefficient tells us that there was an increase of 23 ECMO runs per year, prior to the point of the level effect (2009), and no effect level after this point. In terms of survival, the preslope shows that there was no significant increase before 2009 \((p = 0.41)\), but the level effect was nearly significant within two years \((p = 0.05)\), with a 6% increase in survival. In four years, there was an 8% increase in the survival rate \((p = 0.03)\), and the survival rate increased to 10% six years after 2009 \((p = 0.026)\). The time series of the number of respiratory runs and number of survivors is illustrated in figure 1.

**DISCUSSION**

This study compared two distinct periods of use of ECMO support for respiratory failure: the years before and the years after the 2009 H1N1 pandemic. The increase in the number of pediatric respiratory runs, following a trend since the beginning of the 2000s, was unrelated to the pandemic, according to the ARIMA model. This model, however, suggests that the events that occurred in 2009...
Table 1 - Extracorporeal membrane oxygenation in children in two periods: before and after 2009 (2009 data are compiled until July 2010)

|                          | Runs (n) | Deaths n (%) | Survivors n (%) | Relative risk (95%CI) | Odds ratio (95%CI) | p value |
|--------------------------|----------|--------------|-----------------|-----------------------|-------------------|---------|
| All runs                 |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 2,490    | 1,096 (44.01)| 1,394 (55.9)    | 1.14 (1.07 - 1.21)    | 1.25 (1.12 - 1.39) | < 0.0001|
| July 2010 - July 2017    | 3,290    | 1,268 (38.5) | 2,022 (61.5)    |                       |                   |         |
| Viral pneumonia          |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 365      | 125 (34.2)   | 240 (65.8)      | 1.24 (1.02 - 1.51)    | 1.37 (1.03 - 1.82) | 0.037   |
| July 2010 - July 2017    | 541      | 149 (27.5)   | 392 (72.5)      |                       |                   |         |
| Bacterial pneumonia     |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 303      | 120 (39.6)   | 183 (60.4)      | 1.16 (0.93 - 1.46)    | 1.27 (0.89 - 1.82) | 0.2     |
| July 2010 - July 2017    | 239      | 81 (33.8)    | 158 (66.1)      |                       |                   |         |
| Aspiration pneumonia    |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 42       | 12 (28.6)    | 30 (71.4)       | 0.86 (0.48 - 1.5)     | 0.81 (0.35 - 1.88) | 0.67    |
| July 2010 - July 2017    | 70       | 23 (32.8)    | 47 (67.2)       |                       |                   |         |
| ARDS in postoperative of trauma | |     | | | | |
| July 2001 - July 2010    | 63       | 25 (39.7)    | 38 (60.3)       | 1.09 (0.63 - 1.88)    | 1.15 (0.48 - 2.75) | 0.9     |
| July 2010 - July 2017    | 33       | 12 (36.4)    | 21 (63.6)       |                       |                   |         |
| ARDS nonpostoperative    |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 173      | 79 (45.7)    | 94 (54.3)       | 1.11 (0.87 - 1.41)    | 1.2 (0.78 - 1.84)  | 0.47    |
| July 2010 - July 2017    | 165      | 68 (41.2)    | 97 (58.8)       |                       |                   |         |
| Acute respiratory failure, non-ARDS |   |    | | | | |
| July 2001 - July 2010    | 242      | 102 (42.1)   | 140 (57.9)      | 1.13 (0.94 - 1.35)    | 1.22 (0.9 - 1.66)  | 0.23    |
| July 2010 - July 2017    | 562      | 210 (37.4)   | 352 (62.6)      |                       |                   |         |
| Other respiratory runs   |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 1,336    | 655 (49)     | 681 (51)        | 1.12 (1.04 - 1.21)    | 1.24 (1.07 - 1.43) | 0.004   |
| July 2010 - July 2017    | 1,632    | 714 (43.8)   | 918 (56.3)      |                       |                   |         |
| Veno-arterial runs       |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 1,180    | 588 (49.8)   | 592 (50.2)      | 1.07 (0.99 - 1.16)    | 1.14 (0.98 - 1.33) | 0.1     |
| July 2010 - July 2017    | 1,434    | 668 (46.6)   | 766 (53.4)      |                       |                   |         |
| Veno-venous runs         |          |              |                 |                       |                   |         |
| July 2001 - July 2010    | 853      | 295 (34.6)   | 558 (65.4)      | 1.15 (1.02 - 1.29)    | 1.22 (1.03 - 1.45) | 0.023   |
| July 2010 - July 2017    | 1,897    | 572 (30.2)   | 1,325 (69.8)    |                       |                   |         |

95%CI - 95% confidence interval; ARDS - acute respiratory distress syndrome. The odds ratios refer to the probabilities of survival, comparing the runs in the two periods.

influenced the improvement in survival rates. The overall survival rate increased 6% in the two subsequent years, after having remained relatively unchanged for several decades. When ECMO was used as a rescue therapy for respiratory failure secondary to viral pneumonia, the survival rates improved significantly, from 65.8% to 72.5%. Furthermore, improvements in survival rates were also observed for veno-venous ECMO, increasing from 65.4% to 69.8%. These increments can be attributed, at least partially, to advances in the technology, which included refinement of the double lumen veno-venous cannulas to support a large range of patient sizes with less recirculation, pumps with lower prime volumes, more efficient oxygenators, and changes made in the circuit configuration.

Table 2 - Autoregressive integrated moving average (ARIMA) model

|                          | Estimate coefficient | Standard error | p value |
|--------------------------|----------------------|----------------|---------|
| Pediatric respiratory runs |          |              |         |
| Preslope                 | 23.2                 | 10.6          | 0.049   |
| Level effect (2 years)   | 49.2                 | 82.3          | 0.5     |
| Level effect (4 years)   | 9.2                  | 96.6          | 0.9     |
| Level effect (6 years)   | -30.8                | 121.9         | 0.8     |
| Survival                 |          |              |         |
| Preslope                 | -0.003               | .004          | 0.4     |
| Level effect (2 years)   | 0.06                 | .030          | 0.05    |
| Level effect (4 years)   | 0.08                 | .034          | 0.03    |
| Level effect (6 years)   | 0.1                  | .041          | 0.026   |
Bacterial pneumonia is a frequent etiology of acute respiratory failure requiring ECMO. The mortality in this series was similar to that reported in adults.\textsuperscript{(17)} We observed an increase in survival rates in cases of ECMO use due to this condition, from 60.4\% to 66.1\%, although it did not reach statistical significance. As the number of runs analyzed was low, we suspect that this improvement could be significant with an increase in the number of cases evaluated.

Our study is based on a registry that does not collect information regarding long-term outcomes such as disabilities and quality of life. Therefore, the real impact of ECMO cannot be inferred, and this is an important limitation. We also lack information on other conditions that affect mortality, such as nonpulmonary organ failure, the presence of chronic pulmonary diseases at the time of ECMO treatment, or even demographic data, such as age. The data were self-reported by each institution and not validated by other investigators. Variations in practices may have influenced the results as well, and the clinical database does not include a severity of illness score. However, given the paucity of studies in pediatrics, the ELSO registry has been used to help answer many research questions. The observed improvement in survival detected in the current study can be important in aiding clinicians in patient selection for ECMO support and in counseling families regarding prognosis.

\textbf{CONCLUSION}

The 2009 H1N1 outbreak provided an opportunity for several centers to use extracorporeal membrane oxygenation as a rescue therapy for severe acute respiratory failure in children. In subsequent years, there was a significant increase in the survival rates among children receiving extracorporeal membrane oxygenation for acute respiratory failure related to viral pneumonia and other respiratory illnesses.

\textbf{RESUMO}

\textbf{Objetivo:} Avaliar o impacto no número de casos de oxigenação por membrana extracorpórea e as taxas de sobrevivência nos anos seguintes à pandemia de H1N1 de 2009.

\textbf{Métodos:} Avaliaram-se dois períodos distintos de utilização de oxigenação por membrana extracorpórea como suporte para insuficiência respiratória em crianças, por meio da análise de conjuntos de dados da \textit{Extracorporeal Life Support Organization}. Foram construídos modelos autorregressivos integrados de médias móveis para estimar os efeitos da pandemia. O ano de 2009 foi o ano de intervenção (epidemia de H1N1) em um modelo de séries temporais interrompidas. Os dados colhidos entre 2001 e 2010 foram considerados pré-intervenção e os obtidos entre 2010 e 2017 como pós-intervenção.
Resultados: Em comparação com o período entre 2001 e 2010, o período entre 2010 e 2017 mostrou aumento das taxas de sobrevivência (p < 0,0001), com melhora significante da sobrevivência quando se realizou oxigenação por membrana extracorpórea nos casos de insuficiência aguda por pneumonia viral. Antes do ponto de nível de efeito (2009), o modelo autorregressivo integrado de médias móveis mostrou aumento de 23 casos de oxigenação por membrana extracorpórea ao ano. Em termos de sobrevivência, a curva mostra que não houve aumento significante das taxas de sobrevivência antes de 2009 (p = 0,41), porém o nível de efeito foi próximo à significância após 2 anos (p = 0,05), com aumento de 6% na sobrevivência. Em 4 anos, ocorreu aumento de 8% (p = 0,03) na sobrevivência, e, 6 anos após 2009, a sobrevivência mostrou aumento de até 10% (p = 0,026).

Conclusão: Nos anos após 2009, ocorreu significante e progressivo aumento global das taxas de sobrevivência com oxigenação por membrana extracorpórea para todos os casos, principalmente em razão de melhoras tecnológicas e dos protocolos de tratamento para insuficiência respiratória aguda relacionada à pneumonia viral e a outras condições respiratórias.

Descritores: Insuficiência respiratória; Oxigenação por membrana extracorpórea; H1N1; Vírus da influenza A subtipo H1N1; Influenza humana; Síndrome do desconforto respiratório; SDRA; Pandemias; Taxa de sobrevida; Criança

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