Chapter 5

Extracorporeal Membrane Oxygenation Use in Asphyxiated Newborns Treated with Hypothermia: Review of the Current Evidence

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http://dx.doi.org/10.5772/intechopen.78761

Abstract

Asphyxiated newborns may be hemodynamically unstable during their first days of life. They often present with severe persistent pulmonary hypertension and/or cardiac dysfunction, which may require aggressive supportive management to maintain homeostasis and prevent further brain injury. In the most severe cases, extracorporeal membrane oxygenation (ECMO) may be required to ensure adequate oxygenation, ventilation and cardiac output. However, due to the risk of irreversible brain injury, clinicians often are concerned about offering ECMO to these newborns. Therapeutic hypothermia during the first days of life has become the standard of care for these newborns to improve their prognosis; however, this treatment in itself has been associated with increased hemodynamic instability and coagulopathy. An additional concern with using ECMO in these newborns is the potential increased bleeding risk when continuing the hypothermia treatment during the ECMO course. This chapter reviews the reported feasibility of performing hypothermia during ECMO. We also review the reported outcomes of asphyxiated newborns treated with hypothermia and ECMO and highlight their potential survival without neurodevelopmental impairments. Thus, ECMO should be considered as a therapeutic option for asphyxiated newborns treated with hypothermia.

Keywords: birth asphyxia, brain, extracorporeal membrane oxygenation, hemodynamics, neonatal encephalopathy, therapeutic hypothermia

1. Introduction

Neonatal encephalopathy secondary to perinatal asphyxia is a common condition, with a global incidence varying between 1.3 and 6.6‰ depending on birth location [1]. It is associated with significant mortality (i.e., 23% of all neonatal deaths worldwide) and long-term morbidity, including cerebral palsy and global developmental delay [2–4]. In developed countries, therapeutic hypothermia has become the standard treatment for newborns born at 36 or more weeks of gestational age who have suffered from birth asphyxia and who present with moderate to severe encephalopathy in the first hours of life [5]. Hypothermia treatment has been shown to reduce the risk of death and long-term disability in these newborns [6, 7].

Hemodynamic instability can develop after birth asphyxia and during hypothermia [8], and may be so severe that some of these asphyxiated newborns treated with hypothermia require support with extracorporeal membrane oxygenation (ECMO) [9–11]. First, transient myocardial ischemia and papillary muscle dysfunction due to subendocardial ischemia occur in one-third of asphyxiated newborns [12, 13]. Second, pulmonary vascular resistances in these newborns are high due to hypoxia-induced pulmonary vasoconstriction, and thus pulmonary hypertension frequently co-exists along with the cardiac dysfunction. Acute pulmonary hypertension may lead to a reduction in the right ventricular function, which, if left untreated, subsequently can impair the left ventricular filling, and hence explain a lower cardiac output [14]. In addition, therapeutic hypothermia results in a lower heart rate in these newborns and a reduction of cardiac output, which reflect the adaptation to the decreased tissue demand during hypothermia treatment [15]. Evidence is accumulating that this hemodynamic instability (including hypotension and persistent pulmonary hypertension) and associated metabolic acidosis and hypoxemia have the potential to worsen brain injury in these newborns [16–18], and thus deserve early and optimal management. Therefore, optimizing the hemodynamic profile of these newborns as early as possible is of the utmost importance for decreasing their risk of further brain injury, even if this requires initiation of ECMO.

2. General aspects of neonatal ECMO

The first reported successful use of neonatal ECMO was in 1975 with a newborn who had meconium aspiration syndrome [19]. Since then, the neonatal ECMO field has evolved rapidly along with the indications and contraindications for this therapy. Broadly, ECMO usually is indicated in newborns for disease processes—believed to be reversible—associated with high mortality.

One of the largest randomized clinical trials of ECMO with newborns was undertaken by the United Kingdom collaborative ECMO trial group [20]. This study enrolled a total of 185 newborns with gestational age ≥35 weeks and birth weight ≥2 kg. The main indication for ECMO in this study was severe respiratory failure with an oxygenation index ≥40. The

primary diagnosis was persistent pulmonary hypertension, meconium aspiration, congenital diaphragmatic hernia, sepsis, and idiopathic respiratory distress. The results suggested significant survival benefits for the newborns, who received ECMO, with a relative risk reduction of 0.55 (95% CI 0.39–0.77) ($p = 0.0005$). These results translate into four newborns, who needed to be treated with ECMO for one newborn to benefit from a reduction in mortality.

As of mid-2017, the international extracorporeal life support organization (ELSO) registry reported a total of 35,598 neonatal runs of ECMO worldwide in active centers [21]. The majority of these neonatal ECMO runs were for pulmonary indications (75%) and a smaller proportion for cardiac indications (20%); extracorporeal cardiopulmonary resuscitation (ECPR) constituted only 5% of the total neonatal ECMO runs [21].

Several studies have reported on the short- and long-term outcomes of newborns treated with ECMO (22, 23). Some of these studies have found that newborns treated with ECMO are at an increased risk of death and neurodevelopmental impairments [22, 23]. However, a population-based study, which reported the outcomes of 224 newborns treated with ECMO for various indications between 1993 and 2000, showed that 86% of these newborns survived, and 49% had a normal development in the motor, cognitive, and behavioral domains at 5 years of age. The survival and long-term outcomes of newborns, who received ECMO, have been shown to depend significantly on the underlying disease and the indication for ECMO [24, 25]. For example, newborns with congenital diaphragmatic hernia had lower survival rates and a higher incidence of long-term neurodevelopmental impairments, compared to newborns treated with ECMO for other indications, such as meconium aspiration syndrome [25].

ECMO-related brain injury is a multifactorial process in which factors related to the pre-ECMO illness and events during the ECMO course (including cannulation) play a role [26–30]. During cannulation, a period occurs of decreased blood flow and potential hypoxia when the neck vessels need to be ligated. In veno-arterial (VA) ECMO, the lack of pulsatile blood flow may lead to endothelial dysfunction, which could contribute to the lack of brain autoregulation [29, 30]. In veno-venous (VV) ECMO, even if the carotid artery is spared, a concern exists about venous congestion due to the obstructive nature of the cannula, which can lead to systemic venous congestion and a higher incidence of posterior fossa hemorrhage, compared to patients who are treated with VA ECMO [27, 28]. Thus, although neonatal ECMO has significantly improved the prognosis of some critically ill newborns, it still is associated with a non-negligible risk for brain injury in the treated newborns.

3. ECMO and therapeutic hypothermia

Clinicians raise concern about increased bleeding risk when providing therapeutic hypothermia during ECMO support. However, several studies have reported the short- and long-term outcomes of newborns treated with ECMO and hypothermia without bleeding complications. Hichiba et al. [31] found that newborns with a body weight between 2 and 5 kg, who were treated with ECMO for severe respiratory failure, could receive hypothermia

treatment down to 34°C for 12 h while on ECMO without worsening their survival rate, hemodynamic instability, bleeding risk, and thromboembolic complications. Horan et al. [32] found that newborns who were more than 33 weeks of gestation and who were treated with ECMO for severe respiratory failure could receive hypothermia treatment down to 34°C for 48 h during ECMO without worsening their cardiovascular status, nor having major bleeding. Of note, newborns with severe encephalopathy were excluded from both studies. The safety of maintaining hypothermia down to 34°C during ECMO also was observed in 37 newborns after cardiac surgery by Lou et al. [33]; none of the newborns treated with ECMO and hypothermia developed intracranial hemorrhage or a worsening of hemodynamic instability. In addition, Field et al. [22, 34] found that mild hypothermia down to 34°C could be safely maintained during ECMO for 72 h with newborns with meconium aspiration, persistent pulmonary hypertension, or severe cardiorespiratory failure. When they compared the outcomes at 2 years of age of their 45 newborns treated with mild hypothermia to 34°C for 48–72 h during ECMO to the outcomes of their 48 newborns treated only with ECMO, the mild hypothermia treatment did not improve the outcomes of these 45 newborns [22]. However, given the heterogeneity of the initial diagnoses in this studied population of newborns, these results cannot be extrapolated directly to asphyxiated newborns, in whom hypothermia, not in the context of ECMO, has been shown to be of benefit [6, 7]. Therefore, as of now, no evidence exists that the incidence of significant bleeding and the need for inotropes were worsened when hypothermia was provided to newborns during the ECMO course.

4. Feasibility of ECMO with asphyxiated newborns treated with hypothermia

The major complications during an ECMO course are hemorrhagic and/or thromboembolic, with an increased risk of intracranial hemorrhage. Asphyxiated newborns treated with hypothermia are already at an increased risk of hemodynamic instability, thrombocytopenia, and coagulopathy, which are risk factors for intracranial bleeding [35, 36] and further brain injury [10, 17] (**Figure 1**). These complications may be due to the primary asphyxial event or the consequence of the therapeutic hypothermia [8]. Thus, questions have been raised about whether providing ECMO treatment for these asphyxiated newborns may worsen their outcome and increase their risk of intracranial bleeding.

To date, only a limited number of studies reported on the use of ECMO with asphyxiated newborns treated with hypothermia [9–11]. The Cuevas Guaman et al. [10] study is the largest of these studies, which included 187 asphyxiated newborns treated with ECMO. They did not find any difference in the incidence of bleeding or mortality in the 78 asphyxiated newborns treated with hypothermia during the ECMO course, compared to the 109 not-cooled asphyxiated newborns treated only with ECMO. These two groups also did not differ in their incidence of cardiopulmonary, renal, neurological, and metabolic complications. Therefore, according to the currently limited available evidence, it appears that ECMO therapy may be run safely with asphyxiated newborns treated with hypothermia.

http://dx.doi.org/10.5772/intechopen.78761

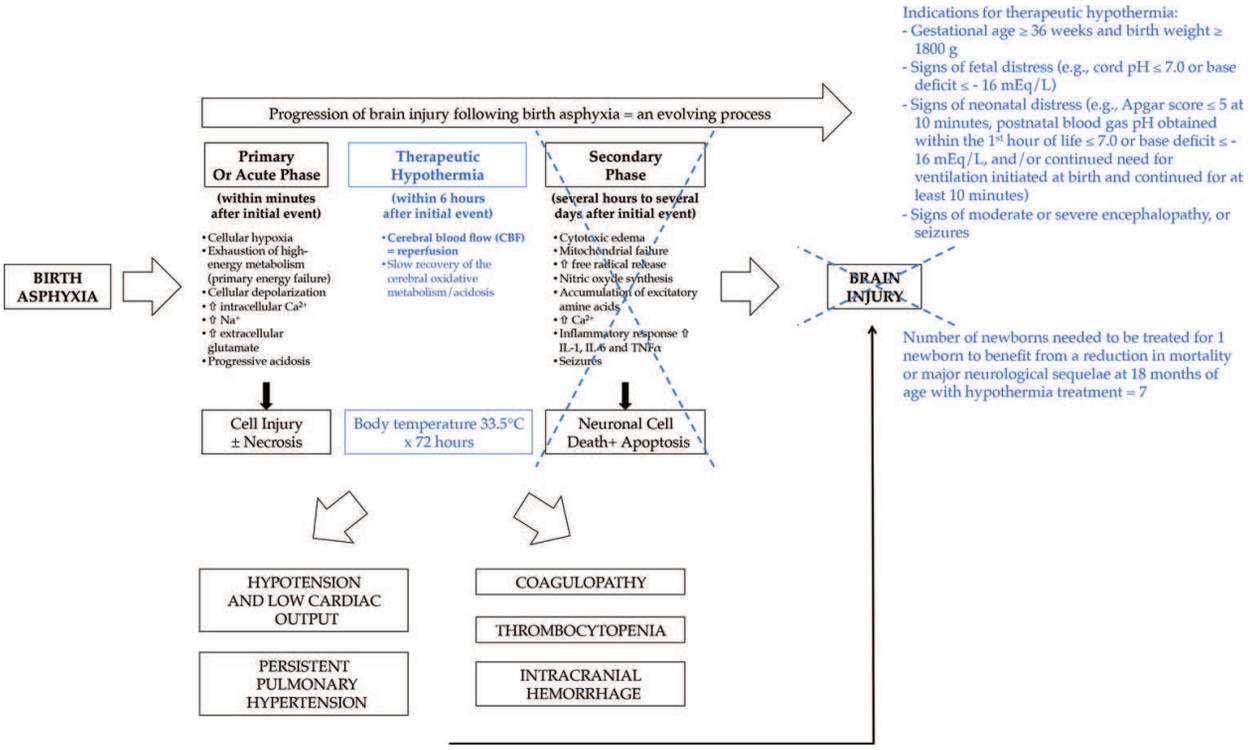

Figure 1. Schematic explaining indications of hypothermia treatment, and potential complications of birth asphyxia and hypothermia.

5. Short- and long-term outcomes in asphyxiated newborns treated with hypothermia and ECMO

Hypothermia treatment has improved the prognosis of asphyxiated newborns, making neonatal encephalopathy a "reversible" condition in one of seven treated newborns [37, 38]. However, due to their risk of irreversible brain injury, clinicians often are concerned about offering ECMO to these newborns [39]. Data on the outcome of asphyxiated newborns who received ECMO during the first 72 h of life are scarce [9–11] (**Table 1**). Shah et al. [11] reported on two asphyxiated newborns treated with hypothermia and ECMO who survived, but they did not mention their outcome. Massaro et al. [9] reported on five asphyxiated newborns treated with hypothermia and ECMO: they all survived and three of them were developmentally age appropriate at follow-up at 6–21 months; one had increased tone at 3 months but then was lost to follow up; and one had significant motor and cognitive delay. Cuevas Guaman et al. [10] studied 78 asphyxiated newborns treated with hypothermia and ECMO and reported a 15% mortality, 22% neurological complications (e.g., brain hemorrhage or infarction), and 12% seizure rate; however, they did not report on the long-term outcomes of these newborns. Thus, current evidence suggests that the outcome of asphyxiated newborns treated with hypothermia and ECMO is not always poor.

In addition, to achieve optimal results, early rather than later consideration of ECMO during the course of therapeutic hypothermia is probably important for these critically ill newborns,

Reference	Number of newborns	Survival rate	Outcomes
Shah et al. [11]	Two asphyxiated newborns treated with hypothermia and ECMO	2/2 (100%) survived	Long-term neurodevelopmental outcome not known
Massaro et al. [9]	Five asphyxiated newborns treated with hypothermia and ECMO	5/5 (100%) survived	• 3/5 (60%) developmentally age appropriate at follow-up at 6–21 months; • 1/5 (20%) increased tone at 3 months but then was lost to follow up; • 1/5 (20%) significant motor and cognitive delay
Cuevas Guaman et al. [10]	Seventy-eight asphyxiated newborns treated with hypothermia and ECMO	66/78 (85%) survived	Long-term neurodevelopmental outcome not known Short-term outcome included: • 17/78 (22%) neurological complications (e.g., brain hemorrhage or infarction) • 9/78 (12%) seizure rate

Table 1. Outcomes in asphyxiated newborns treated with hypothermia and extracorporeal membrane oxygenation (ECMO).

since a prolonged duration of metabolic acidosis, inotropic support, and a need for inhaled nitric oxide prior to ECMO initiation have been associated with a higher rate of bleeding complications [40, 41], and since hemodynamic instability has been associated with worsened brain injury in those newborns [16]. In addition, it may be safer to start ECMO, if required, before the rewarming phase following the 72-h hypothermia treatment, so to allow hemodynamic support during this time-period when pulmonary hypertension crises are more likely to occur [11].

6. Considerations for using ECMO in asphyxiated newborns treated with hypothermia

ECMO is an expensive and labor-intensive, life-sustaining modality. The ideal candidate for ECMO is a patient with a reversible disease condition for whom standard treatments have failed to reverse the disease process and for whom mortality risk is high. The most common contraindications for neonatal ECMO currently include a gestational age less than 34 weeks, weight of less than 2 kg, significant coagulopathy, significant intraventricular hemorrhage, and an underlying genetic condition with a poor prognosis [42]. Severe metabolic acidosis prior to ECMO also is considered a relative contraindication for ECMO, since this has been associated previously with higher mortality and brain injury [43]. However, the successful use of ECMO has been reported for a newborn with persistent pulmonary hypertension, presumed sepsis, and a pre-ECMO pH of less than 6.6 [44]. Thus, asphyxiated newborns treated with hypothermia—if they do not present with intraventricular hemorrhage or proven severe and irreversible brain injury at the time of cannulation—should be eligible for ECMO.

http://dx.doi.org/10.5772/intechopen.78761

If started in an optimal timeframe, ECMO associated with hypothermia treatment may ensure adequate oxygenation, treat catecholamines-resistant hypotension, and minimize further brain injury in these newborns, without causing intracerebral hemorrhage if coagulopathy can be kept under control.

7. Conclusions

In conclusion, ECMO might thus be considered as a therapeutic option for asphyxiated newborns treated with hypothermia, if they need it respiratory or hemodynamic support, if they have no proven irreversible brain injury visible at the time of starting ECMO.

Acknowledgements

We thank Mr. Wayne Ross Egers for his professional English correction of the manuscript.

Conflict of interest

The authors declare no competing financial interests. No honorarium, grant, or other form of payment was received for the preparation of this manuscript.

Funding

Pia Wintermark receives research grant funding from the FRSQ Clinical Research Scholar Career Award Junior 2 and a CIHR Operating Grant.

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