Case Report
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Whole body hypothermia treatment and results in newborns with perinatal asphyxia: a case series.

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Hypoxic ischemic encephalopathy (HIE) secondary to asphyxia clinically manifests as acute or sub-acute brain injury. Out of all newborns with HIE, 15-20% die in the postnatal period, while 25% sustain severe and permanent neurological damage (cognitive delay, cerebral palsy and epilepsy). Early application of whole body hypothermia therapy (the lowering of body temperature to 33.5-34°C) has been shown to lower disability and mortality rates in newborns with HIE. To date, we have used therapeutic hypothermia in 7 neonates born in our clinic with severe asphyxia. One of the patients died; 6 have been discharged and are showing normal neurological, mental and physical development.

Keywords: newborn, perinatal asphyxia, hypoxic ischemic encephalopathy, therapeutic hypothermia

Introduction

Perinatal hypoxic ischemic encephalopathy (HIE) is seen in every 3-5 full-term live births out of 1000 [1]. HIE secondary to asphyxia clinically manifests as acute or sub-acute brain injury. The main causes of HIE are systemic hypoxemia and low brain blood flow [2-4]. Out of all newborns with HIE, 15-20% die in the postnatal period, while 25% develop severe and permanent neurological deficit (cognitive delay, cerebral palsy and epilepsy). Early application of whole body hypothermia therapy (the lowering of body temperature to 33.5-34°C) has been shown to lower disability and mortality rates in newborns with HIE. ILCOR has recommended therapeutic hypothermia as first line treatment for moderate and severe HIE in full-term or late preterm neonates since 2010 [6, 7] Experimental studies have demonstrated that lowering the brain temperature by 2-3°C after hypoxic ischemic damage slows down the energy metabolism and reduces neuronal death [8]. As far as our knowledge goes, whole body hypothermia has never been used in our country before. The aim of this report is to present the results of our application of this method to treat newborns with severe and moderate HIE since November 2015.

Materials and Methods

Whole body hypothermia was used in 7 patients born at our clinic between November 2015 and June 2016. The treatment was administered with the non-invasive HICO-HYPOTHERM 550 temperature management system.

Treatment was started in patients based on the following AAP criteria: gestational age $\geq$ 36 weeks, age $\leq$ 6 hours, 10 minute Apgar score $\leq$ 5, the need for resuscitation for 10 minutes after birth, cord blood pH <7.0 or BE $\geq$-16 mmol/l, clinical signs of moderate or severe encephalopathy, seizures or abnormal activity on EEG (9).

The patient group was comprised of newborns that fulfilled at least 3 of the above criteria. Treatment was started in all patients within the first hour of life; body temperature was lowered to 33.5-34°C and raised back to normal after 72 hours.

Patients had gestational ages of 38-40 weeks, 1 minute Apgar scores of 3-5 and 5 minute Apgar scores of 3-6. Acidosis was observed in blood samples of all patients (pH $\leq$ 7.0; BE >-16). Three patients had meconium-stained amniotic fluid. One patient had 3rd degree HIE, 4 - 2nd degree HIE, and 2 - 2-3rd degree (Table 1).

Table 2. Laboratory parameters of cases

New born #	Gestational Age, Weeks	Apgar score		Initial blood sample			Encephalopathy degree	Clinical seizures	Seizures on EEG
		1 min	5 min	pH	BE	Lactate			
1	40	1	5	6,8	-20	12	2-3	-	+
2	40	3	6	7,0	-17	10,8	2	+	+
3	39	2	4	6,9	-25	>15	2	-	-
4	38	1	5	7,0	-21	-	2-3	-	-
5	38	3	6	7,0	-18	13	2	+	+
6*	38	1	3	<6,8	-	>15	3	+	+
7	39	1	4	6,9	-23	>15	2	-	-

**This patient was transferred to another hospital on postnatal day 8 and died there during follow-up.*

Results

All patients who underwent therapeutic hypothermia were born via natural labor. In all cases, initial resuscitation procedures were carried out and treatment was started within one hour. During the 72-hour treatment, ECG showed sinus bradycardia in 5 patients. Clinical seizures were observed in 3 patients, while 4 had abnormal activity on EEG. Neurosonographic examination revealed no abnormalities. Eye fundus examination showed subretinal hemorrhage in 4 patients. Based on the clinical tableau and EEG results, 4 patients were started on phenobarbital. Six patients were discharged following 72 hours of treatment with normal neurological outcome. Regular follow-up exams of all six continue to show normal physical, mental and neurological development. On postnatal day 8, the intubated patient with the poorest clinical tableau and blood test results was transferred to another clinic as per the wishes of the family, where he died during follow-up.

Discussion

Neonatal deaths represent 41% of all annual pediatric deaths under the age of 5. A quarter of these occur in the first week of life. Various birth complications are the main causes of neonatal death (10). Approximately 25% of neonates born with cord blood pH<7 suffer permanent neurological damage and death (11). The perinatal brain is particularly susceptible to hypoxic ischemia, cerebral palsy and the resulting permanent damage (12). Asphyxia has a major impact on neonatal morbidity and mortality and developmental prognosis (5). Therapeutic hypothermia is the only currently known treatment that has been shown to improve neurological outcomes and disability and mortality risks in neonates with hypoxic brain injury. Hypothermia treatment was first used in newborns in 1960, and research and trials in the following decades demonstrated the efficacy of hypothermia in protecting the brain from the effects of perinatal oxygen deprivation.

As far as knowledge goes, the neonatal intensive care unit at our clinic is the pioneer of this treatment method in the Azerbaijan Republic. Of the 7 patients who were treated, 1 died after being transferred to another hospital and 6 were discharged within a week with regular follow-up showing no mental or physical delays. The EEGs of patients who initially showed abnormal activity have now reverted to normal and phenobarbital has been gradually reduced and stopped. All cases of subretinal hemorrhage in the neonatal period have now shown reabsorption.

In conclusion, therapeutic hypothermia in neonates with hypoxic ischemic damage is a demonstrably effective line of treatment that merits wider implementation.

Conclusion

Based on the results of hypothermia treatment trials run in our clinic and similar results reported worldwide, we can conclude that hypothermia is the most effective currently known method of treating neonates with hypoxic ischemic encephalopathy.

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