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Neonatal Hypoxic-Ischemic Encephalopathy and Hypothermia Therapy: Solving Questions about Monitoring and Prognosis

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Abstract

Introduction: The hypoxic-ischemic encephalopathy is a significant cause of neurologic morbidity and mortality in the newborn. One of the standards of management is the hypothermia therapy that allows a reduction in the brain injury extension, making important to define the settings involving the admission to such therapy.

The hypothermia therapy protocol demands an strict compliance of the inclusion criteria, one of them, the APGAR score at a determinate moment, no protocol includes its score at different times, the APGAR score helps the clinician to decide the therapeutic approach of this patients, and the tenth minute score has received priority over the other minute's score, nevertheless many patients will lose the opportunity to be admitted for hypothermia therapy when this score is taken, although the ACOG has determined that it is the minute 5 APGAR that has the value to define neonatal asphyxia, most European and American protocols take the 10 minute APGAR score; besides it is possible that the newborn in the first 6 hours does not demonstrate the secondary damage, or energy failure that are generated up to 48 hours later, in which the use of hypothermia therapy has truly a therapeutic effect. Then it is imperative to analyze the early outcomes according to the APGAR in the minute 5 and 10 in patients admitted for hypothermia therapy.

Methods: A descriptive study, and retrospective analysis of a cohort of 62 patients born in term with hypoxic ischemic encephalopathy, admitted at the intensive care unit of Clinica Universitaria Bolivariana, Medellin, Colombia, between 2014-2016.

Results: The cohort of newborns exhibits a mortality of 8.1%, which was significantly associated with the presence of complications during hypothermia. The most frequent pattern found in the electroencephalographic line during the first day was suppression burst 45.2%, and heading to the end of the protocol, 51.6% achieved normalization; imaging findings such as the subcortical ischemia was the mostly found in 25.8%, but the hemorrhagic ones were only found in 12.9%. During a bivariate analysis a correlation between different outcomes were found, the most important of them, was the one among the presence of status during the electroencephalographic monitoring with an APGAR score under 5 at the fifth minute.

Conclusions: It is important to take on consideration the five-minute APGAR score because of its relation with epileptic status development, which in our cohort was more frequent without clinical manifestation than with it during monitoring. This is important because of the negative prognosis that this implies in the short term, in addition the patients that presented epileptic status post medication had correlation with persistent abnormalities at the discharge, that is why the five-minute APGAR score under five can predict the neurological examination at the discharge and the epileptic status development as a predictive marker. This also creates a suspect that the recommendation to use hypothermia therapy without electroencephalographic monitoring is a dangerous practice, and makes it difficult to assess the response to it.

Keywords: Newborn; Hypoxic-ischemic encephalopathy; Mortality; Neonatal seizures

Introduction

The ischemic hypoxic encephalopathy (HIE) is an entity produced as a consequence of a newborn's brain's oxygen supply reduction, preceded by hypoxemia or ischemia [1], being one of the main causes of alterations in the short, mid and long term in the neurodevelopment [2].

In our milieu, incidence and mortality of the condition are both unknown, but different studies show a 1.088 per 1,000 alive infants [3], furthermore a mortality that fluctuates between 13-15% [4,5] is reported, and up to a 10% death risk increase in patients with mild encephalopathy [2].

Different methods have been established for the entity handling. One of them is the cooling therapy, that initiated within the first 6 hours after birth and continued for 72 hours, allows to reduce the rate of death or moderate to severe disability in term newborns with HIE, reducing the cerebral lesion extension [2], and the development of chronic neurologic alterations with an NNT 7 [6]. For such therapy a

strict protocol is established, so patients' continuous monitoring and vigilance can take place. Additionally, choosing the right anticonvulsant becomes a crucial decision for handling this kind of patients, since convulsions are the greatest impact prognosis comorbidity. Currently, Phenobarbital and Phenytoin are among the options to be taken into consideration, which effectiveness is incomplete when it comes to controlling the crises [7], and even the first one has been linked to subsequent convulsion incidence and morbidity increases when administered in the early stages [8]. The other therapeutic evaluated options are medications such as Levetiracetam and Topiramato that are becoming more relevant during the treatment, finding an adequate control in 89% of the administered patients during the first 24 hours, but it is not yet recommended internationally because their use in newborns is still "off label" in most of the countries they are available [9].

Hypothermia therapy is the only current therapeutic choice to treat HIE, having said that, it is very necessary to make clear the admission terms for such therapy, but that is not reflected in numerous scientific publications in which both the Base excess value and the APGAR score are very variable at the time of scoring. We want to analyze, in the following study, the criteria used in our unit and the impact that such criteria have on the patients' early prognosis, evaluated with standards such as the development of neonatal ictal progression events, imaging and polysomnographic abnormalities and also the abnormal neurologic examination at the time of discharge.

For this purpose, a retrospective cohort analysis is done to ischemic hypoxic encephalopathy admitted patients at the Neonatal ICU at Clínica Universitaria Bolivariana (reference unit in the region), in the years 2014 to 2016. Such patients were admitted at cooling protocol.

Methods

This is a descriptive study, retrospectively analyzing a patient's cohort, where investigators revise clinical histories and collect data from admitted patients at the Universidad Pontificia Bolivariana's intensive care unit, from 2014 to 2016, presenting ischemic hypoxic encephalopathy admitted at hypothermia protocol.

Inclusion criteria

- Newborn>36 weeks and at least 1800 gr of weight+1 of the following:
  - APGAR<5 at the first 10 minutes of resuscitation
  - Umbilical cord or arterial pH<7 at the first hour
  - Base deficit>16 mmol/L of mbilical cord or obtained in the first 60 minutes.
  - ICD 10 codes used: P91.60 Hypoxic ischemic encephalopathy; P914 neonatal cerebral depression; P9160 Hypoxic ischemic encephalopathy (HIE), unspecified.
  - Admittance at the intensive care unit for hypothermia therapy
  - Available data.

Exclusion criteria

Patients needing hypothermia therapy for other purposes, insufficient data

Ethics

This project abides by scientific, technical and administrative rules for health investigation designated by Resolution 8430 signed on October 4th 1993 of the Ministerio de Salud de Colombia (Colombia's Health Ministry). In addition, the project also abides by the ethical standards proposed by the World Medical Association of Helsinki (Table 1).

According to the defined criteria in Section 11 of the Resolution 8430 signed in 1993, this investigation is classified as "no risk", because documentary research techniques and methods will be used, and no intervention nor intended modification of the biological, physiological and social variables will be done on the individuals that will participate in such investigation.

The process through which information was obtained consisted of the data collected from the clinical history with which a previously designed format was filled out. Every patient's clinical and epidemiological information were merely used for scientific and academic purposes, duly based on the research goals.

Results

Regarding the sociodemographic variables, most population was male (74.2%), in average born term pregnancies, with normal size and weight for gestational age, 68.8% born through the birth canal, of which 59.7% came from Valle de Aburrá.

	n (%)
Sex	Female 16 (25.8%)
	Male 46 (74.2%)
Procedence	Outside of Valle de Aburra 25 (40.3%)
	Medellín 23 (37.1%)
	Rest of Valle de Aburra 14 (22.6%)
Health insurance	Alianza 20 (32.3%)
	Others 16 (25.8%)

	Sura 11 (17.7%)
	Coosalud 8 (12.9%)
	Coomeva 7 (11.3%)
	Media (SD)
Gestational age (Weeks) n=62	38,371 (1.333)
Weight (Kilograms) n=61	3,049 (0.421)
Size (Centimeters) n=36	49,666 (2,177)
Institutional delivery	Yes 13 (21%)
(At the Clinica Universitaria Bolivariana)	No 49 (79%)
	Vaginal 34(54.8%)
	Cesarean 15 (24.2%)
	Vaginal+Forceps 9 (14%)
Maternal delivery	Unknown 4 (6.5%)
	Yes 2 (3.2%)
	No 58 (93.5%)
Preeclampsia	Unknown 2 (3.2%)
	Yes 4 (6.5%)
	No 56 (90.3%)
Intra Uterine infection	Unknown 2 (3.2%)
	Yes 21 (33.9%)
Long labor final stage	No 41 (66.1%)
	Yes 3 (4.8%)
Umbilical cord prolapse	No 59 (95.2%)
	Yes 7 (11.3%)
Neck double Knot	No 55 (88.7%)
	Meconium I 2 (3.2%)
	Meconium II 4 (6.5%)
	Meconium III 1 (1.6%)
	Others 10 (16.1%)
	Normal 3 (4.8%)
Amniotic fluid characteristics	Unknown 42 (67.7%)

Table 1: Socio-demographic characteristics.

Sentinel events, clinic history such as umbilical cord prolapse, neck double knot appeared in low proportion (14.5%), and long labor final stage was a 33.9%, while maternal stroke and placental abruption were absent.

The most representative findings are presented in Tables 2 and 3. Including the bivariate analysis results obtained after crossing different outcomes in relevance to the decision of the beginning of hypothermia therapy.

	n (%)
EEG pattern at day 1	Abnormal discontinuous: 13 (21%)
	Suppression Burst: 28 (45.2%)
	Wake up-sleep cycle: 2 (3.2%)
	Uninterpretable: 19 (30.6%)
EEG pattern at day 2	Abnormal discontinuous: 26 (41.9%)
	Suppression Burst: 14 (22.6%)
	Wake up-sleep cycle: 3 (4.8%)
	Continuous low voltage: 1 (1.6%)
	Uninterpretable: 16 (25.8%)
	Unknown: 2 (3.2%)
EEG pattern at day 3	Abnormal discontinuous: 27 (43.5%)
	Suppression burst: 10 (16.1%)
	Wake up-sleep cycle: 8 (12.9%)
	Uninterpretable: 15 (24.2%)
	Unknown: 2 (3.2%)
EEG pattern at the end	Abnormal discontinuous: 10 (16.1%)
	Suppression burst: 6 (9.7%)
	Wake up-sleep cycle: 32 (51.6%)
	Uninterpretable: 12 (19.4%)
	Unknown: 2 (3.2%)
Seizures at the EEG	Yes: 26 (41.9%)
	No: 19 (30.6%)
	Uninterpretable: 15 (24.2%)
	Unknown: 2 (3.2%)
Status at the EEG	Yes: 11 (17.7%)
	No: 34 (54.8%)
	Uninterpretable: 15 (24.2%)
	Unknown: 2 (3.2%)
Number of seizures in all monitoring	Media(SD)
	23.961 (23.123)

Table 2: Electroencephalographic characteristics during hypothermia protocol.

Outcome 1	**Outcome 2**	**OR (CI)**	**p**
Mortality	Complications during hypothermia protocol	10.4 (1.49-74.68)	0.091
Abnormal neurological findings at the hospital discharge	Post medication epileptic status	5 (1.01-27.46)	0.109

Need of anticonvulsant drugs at hospital discharge	Clinical seizures	3.58 (1.12-11.34)	0.05
Needing of anticonvulsant drugs at hospital discharge	Post medication epileptic status	14 (1,96-126,56)	0.01
Epileptic status development	Tonic or clonic seizures	5.25 (1.17-23.78)	0.08
Epileptic status development	Sepsis	8.16 (1.18-71.17)	0.029
Status during electroencepalographic monitoring	Clonic seizures n=43	5.83 (1.27-26.93)	0.05
Status during electroencepalographic monitoring	APGAR score<5 at the fifth minute n=37	57 (1.06-33.6)	0.1
Status during electroencepalographic monitoring	APGAR score<5 at the tenth minute n=29	11.33 (1.91-67.78)	0.01

Table 3: Correlation between outcomes.

Discussion

The hypothermia therapy protocol demands a strict compliance of the inclusion criteria, one of them, the APGAR score at a determinate moment, no protocol includes its score at different times; besides it is possible that the newborn in the first 6 hours does not demonstrate the secondary damage, or energy failure that are generated up to 48 hours later, in which the use of hypothermia therapy has truly a therapeutic effect [10]. This shows the importance of analyze and study such criteria to impact the neurodevelopment of the patients with this disease.

The sentinel event was only clearly identifiable in 14.5% of the cases, basically prolapse and neck double knot, the rest of the patients did not present a clear sentinel marker according to the ACOG definition [11]. Similar percentages have been demonstrated in other studies, in which the basal cause is not identified for multiple reasons, therefore extension studies are needed, such as placenta and cord pathology, that is currently performed as a routine protocol in many health centers.

In our unit, half the patients achieve a normal electroencephalographic record at the time of suspending the hypothermia therapy, regardless of the background rhythm they had at the beginning of such therapy. Although we cannot make a statistical inference, we can demonstrate in some cases, EEG normalization after 72 hours but changes to an abnormal discontinuous record for an EEG at the time of suspending therapy and completing overheating. The significance of such finding is not clear yet, but it will be taken into consideration in further studies.

Additionally, the sepsis diagnosis associated with a more threatening HIE [12], besides in our study, an increase of eight times more was noticeable in regard to patients without sepsis, from the risk of presenting an epileptic status with or without clinical manifestation, once the anticonvulsant medication is administered. The relation between such status and the prognosis worsening could be an obvious conclusion, but it is not possible to determine whether this is why the sepsis has demonstrated to be one of the greatest and the most persistent factors of poor prognosis in different HIE and hypothermia studies. However, the risk increase is great enough to establish in our protocol that the patients with sepsis diagnosis undergo a more prolonged electroencephalographic monitoring even in the absence of clinical crises.

In our opinion, one of the most relevant findings is associated with the risk of presenting epileptic status according to the APGAR scoring. As it has been described before, the APGAR criterion, at the time of admitting a patient at hypothermia therapy, has been a disagreeing point among the criteria in societies like ACOG for perinatal asphyxia, and the chosen ones for hypothermia classic studies, since the first one takes into account the APGAR at 5 minutes, and the second one at 10 minutes [13]. However, the fact that we found out that the APGAR at 5 minutes lower than 5 increases the risk of presenting epileptic status 57 times above normal APGAR score, it is good enough to choose the APGAR score at 5 minutes as an admission criteria at Hypothermic therapy. On the other hand, the APGAR score at 10 minutes lower than 5 only increased the risk of Status 11 times, which is very likely to be related to the severity of cerebral damage where there would not be ictal progression events but there would be burst-suppression. We consider that this information is highly relevant, mostly for those protocols in which the APGAR at 5 minutes is not taken into account [14,15].

In regard to abnormalities persistence during the discharge neurological examination, once again the epileptic status, with or without clinical manifestation, is the one that showed a significant increase in the risk of presenting abnormalities. This risk even exceeded the one generated by the APGAR score, the pH values, Base excess, and the HIE stage. The above once again leads us to create a hypothesis: among the valuable variables, the main marker of poor prognosis after the hypothermia therapy is the presence of epileptic status.

Furthermore, the presence of epileptic status, with or without clinical correlation, increased the risk of presenting lesions in the basal ganglia in the post therapy resonance, four times above the other electrical patterns.

Findings such as the degree of acidosis and its absence related with the discharge abnormal neurological exam, and neither electroencephalogram at the time of discharge, lead us to suspect that once the hypothermia is started, all these markers that indicate the Hypoxia severity, lose their capacity to determine prognosis, and it would only be the electroencephalographic finding the one that would answer the question regarding this therapy, and the risk of persistent abnormalities. This is why the use of EEG monitoring during and several days after therapy, is fundamental in our institution. Even more important is the fact that the absence of electro clinical correlation, or in other words, the electric ictal progression augmented the risk of persistent abnormalities in the neurological exam at the time of discharge, but not the ictal event with electro clinical correlation, giving the EEG monitoring during and after the hypothermia therapy even much more power and importance, being the electrophysiology and not the clinic one, the standard response to the therapy and the prognosis at the time of discharge.

To sum up, we consider that the most relevant data is this study fully support the necessity that hypothermia therapy be spread around all neonatal units in the world, that can also count on the possibility of complexity monitoring, including the aEEG, and performing extension studies, besides the possibility of outpatient follow-up.

Conclusion

Nowadays HIE has an effective treatment and easy administration such us hypothermia therapy, but is necessary to count on enough technology to guarantee the a EEG monitoring during and after the therapy, because the events presented in this monitoring are most likely to be the principal prognosis markers. Additionally we left to readers' consideration the recommendation of using the 5 minute APGAR score better than the 10 minute score in the admission criteria for the therapy because of the important correlation between epileptic status development and the APGAR score aforementioned, being the epileptic status another marker for neurologic prognosis that can influence the hypothermia therapy.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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