Universitat de Girona
Facultat de Medicina

CEREBRAL OXIMETRY AS A PREDICTOR OF EARLY OUTCOME IN NEWBORNS WITH HYPOXIC – ISCHEMIC ENCEPHALOPATHY

FINAL DEGREE PROJECT

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Una persona es el resultado de la siguiente fórmula:
***V= (c + h) x a**; donde la C son conocimientos, la H habilidades y la A es la actitud. Lo importante de ésta, es que la C suma, la H suma, pero la A multiplica.*
Ante una situación complicada, uno tiene dos opciones; resignarse o luchar contracorriente para vivir con ilusión.
Victor Kuppers.

https://www.youtube.com/watch?v=_8UxsRHp004

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ABBREVIATIONS

- aEEG: amplitude electroencephalogram
- Bpm : beats per minute
- ENE: neuronal enolase
- FC : cardiac frequency
- HIE : Hypoxic ischemic encephalopathy
- IL 6: interleukin 6

ABSTRACT

Hypoxic-ischemic encephalopathy (HIE) is a major cause of greater neonatal morbimortality and permanent disability. Its incidence is 1,6 of 1000 live newborns and it is higher in developing countries.

Nowadays, it is not possible to know the prognosis with certainty of newborns with HIE. We have tests and classifications which help us in the prognosis but still, the outcome is uncertain.

Cerebral oximetry is a non-invasive and simple test which could help us to know more precisely the severity of the brain damage and the future prognosis of the infant. Our objective is to analyze if the values of the cerebral oximetry have prognostic value in HIE using a defined protocol.

This is a descriptive study and it will take place in six hospitals in Catalunya and it will last three years in order to get the sample size needed. We will study 69 patients with different grades of HIE following a non-probabilistic, consecutive sampling.

We will study if cerebral oximetry´s values can predict the early outcome of hypoxic-ischemic encephalopathy in neonates measured in ranges which are pathological (<55% and >90%) and normal ranges (55% to 85%) and secondary, we will analyze if more pathological values in cerebral oximetry are associated with those electroencephalographic paths which are related to the worst outcome as discontinuous, burst-suppression and convulsions and if more pathological values in cerebral oximetry are translated into greater brain affectation in magnetic resonance and sequels risk.

We will record data (sex, gestational age, pH, temperature, aEEG, cerebral oximetry values, renal oximetry values, and magnetic resonance results) hourly for 96 hours from the birth and we will analyze it using descriptive analysis, bivariant analysis and multivariant analysis.

INTRODUCTION

INTRODUCTION

1. INCIDENCE OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Hypoxic-ischemic encephalopathy in neonates is one of the causes of greater neonatal morbimortality and permanent disability. (1,2)
In 2010, the World Health Organization estimates that 96% of 1,15 million neonates with HIE were born in countries with low or moderate rent per capita. (3)

In the last thirty years, it seems the incidence has diminished in developed countries, which could be related to its role as obstetric perinatal attention indicator of almost term or full term fetus(1)(3).Both fetal and maternal security has improved by means of perinatal controls such as cardiotocography registers or meausuring fetal scalp´s pH. (4)

The global incidence rate of HIE (mild to severe) in European countries and the United States varies between 1 to 8 of 1000 newborns although it depends on the definition of HIE and the type of the study which is accomplished.
Revision article showed that the average incidence is 1,6/1000 newborns being 60% of the cases from moderate to severe. (5)

In Spain, the distribution of the cases of HIE in autonomous communities is quite homogeneous and severity graduation is similar but there are still some mistakes because 20% of newborns with mild HIE receive hypothermic treatment which is reserved from moderate to severe cases. (5)

The mortality rate in Spain between 2012-2013 in neonates with HIE moderate to severe excluding those who died a few hours after delivery is 16% which is a similar porcentage to other countries comparable to ours.(5)

2. HYPOXIC-ISCHEMIC ENCEPHALOPATHY

2.1. DEFINITIONS

Nonrreasuring fetal status is a term used when there are alterations in a cardiotocographic register and / or fetal acidosis. (6)

Sentinel hypoxic event includes acute incidents around delivery which are able to damage a fetus without neurological affection. When they have clinical translation it helps to define the moment of the aggression and it is necessary to treat it finishing the gestation to avoid neurological damage.(6,7)

Perinatal asphyxia is fetal or neonate damage because of the lack of oxygen or correct tissue perfusion. Hypoxemia, hypercapnia and metabolic acidosis appear because of hypoperfusion.
When the episode is severe enough to damage the neonate´s brain, the newborn suffers in the early hours of life a neurological syndrome named *hypoxic-ischemic encephalopathy* that defines clinical signs and symptoms representing abnormal brain function.(6,8)

2.2. ETIOLOGIES

If one of the following events in table 1 appears, we cannot diagnosticate the newborn as an HIE because all of them are risk factors that can produce asphyxia but it does not mean that it mandatorily occurs.(6)

***Table 1: Risk factors of asphyxia* (6)**

Premature placental abruption	Uterine rupture
Previous vasa	Cord prolapse
Fetal bleeding	Fetus-Matern hemorrhage
Amniotic liquid embolism	others

2.3. PHISIOPATHOLOGY

One of the events described before can lead to fetal or newborn asphyxia which involves the fall of oxygen in the blood or lack of cerebral perfusion.
Newborn´s brain is especially susceptible to hypoxic aggression because it has a big amount of oxygen consume, more quantity of water, a little concentration of antioxidants and less neuronal myelinization.
The damage is multifactorial, provoked by different mechanisms like excitotoxicity, inflammatory response, oxidative stress, apoptosis, and posterior neurogenesis.

Hypoxic-ischemic damage phases can be divided as follows: acute phase, latent phase, secondary phase and tertiary phase.

In the acute phase which starts in the first minutes after the damage, oxygen and glucose drop causes depletion of energy compounds such as triphosphate adenosine and phosphocreatine which are needed to maintain cell metabolism.

This process provokes that sodium and potassium bombs fail as well as neuronal depolarization.
Amino-acids are not recaptured and its concentration rises in synaptic endure causing excitotoxicity.
During this acute phase, sodium and chlorine accumulate in the cells dragging water inside them which can lead to neuronal death.
After that, cell and tissue perfusion and metabolism seem to recuperate although in the latent phase this is transiently.

This phase is related to a decrease in electroencephalogram activity and oxygen consumed, although in magnetic resonance cellular metabolites are normal. The phase lasts between six to twenty-four hours, which is our therapeutic window to treat it, and the shorter this period is, the more severe the brain damage is.

The second phase starts with an increase of lactate levels in the brain and mitochondrial failing as regulator of cell death through apoptosis. Mitochondrial damage can produce oxidative metabolism decoupling which triggers edema, cerebral hyper-perfusion and cell death.

Finally, the tertiary phase occurs, and it is responsible for permanent damage that will last until adult age. The persistence of brain lactic acid, gliosis and the activation of inflammatory receptors and epigenetic changes are related to neurodevelopment problems. Its duration varies from months and years after ischemic damage and predisposes the patient to worsts results. (9–11)

Neurogenesis occurs because cell and tissue damage produced after hypoxia could be general and affects neurological niches which are in the central nervous system. From twenty- four to forty-eight hours after moderate-severe hypoxia, an extensive cell death which affects mainly progenitor neuronal and oligodendrocyte cells, is produced in the subventricular area. (11,12)
There is a different vulnerability among cell types in the subventricular area depending on the place in which they are located and it is seen greater survival in the medial zone. It was used flow cytometry to quantify the proportion of each cell type. It was determined that progenitor neuronal cells decreased and multipotential progenitor cells and glial progenitor cells increased which confirms that HIE changes the subventricular area composition.
Later, cells that migrate from the subventricular area will differentiate in the same proportion in neurons, astrocytes and oligodendrocytes although most of them will have died before getting mature.
It is not confirmed that new oligodendrocytes could produce myelin while the gain of reactive astrocytes increases the production of extra cell-matrix which could inhibit oligodendrocyte differentiation and limitate myelin synthesis.(13,14)

2.4 SYMPTOMS AND SIGNS IN NEWBORN

Hypoxic-ischemic encephalopathy is a syndrome that defines clinical manifestations of abnormal brain function and it is characterized by alteration of wakefulness, breathing difficulty, muscular tone alteration, reflex and motor alteration, the difficulty of deglutition and often seizures. (6)

There are different grades of severity according to neurologic damage which are defined in Sarnat Classification (table 3) and Amiel-Tison and Ellison classification (table 2).

Amiel-Tison and Ellison seem to have more predictive value to predict posterior sequels.

According to Amiel-Tison and Ellison patients with grade 1 of HIE do not usually develop a disability. Patients classified as grade 2 improve during the first week of life but 20% of them presents alterations of muscular tone and delayed psychomotor development. The 50% to 75% of the patients classified as grade 3 die and the percentage of those who survive suffer important sequels.(15)

Table 2 Amiel-Tison and Ellison classification(15)

	Stage 1	Stage 2		Stage 3	
Consciousness	Hyperexcitability	Lethargy or stupor		Comma	
Muscular tone	Upper hypotony	Hypotony		Hypotony	
Osteotendinous reflexes	Exaggerate	Diminished		Diminished or absent	
Suction	Normal	Weak		Difficult or absent	
Deglutition	Normal	Normal or difficult		Difficult or absent	
Moro	Normal/exaggerate	Weak		Absent	
		A	B	A	B
Ocular-cephalic reflexes	Present	**Present**	Present	**Present**	Absent
Breathing	Present	**Present**	Present	**+apnea**	Absent
Seizures	No	**No**	Isolated	**Repetitive or status**	Repetitive or status

Hypoxic-ischemic encephalopathy *Table 3 Sarnat classification* (16)

	MILD	MODERATE	SEVERE
Consciousness	Hiperalert	Lethargic	Stuporous
Muscular tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermitent decerebration
Stretch	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong	weak	Absent
Oculovestibular	Normal	overactive	Weak/absent
Tonic neck	Slight	Strong	Absent
Autonomic function			
Pupils	Mydriasis	Miosis	Variable
Heart rate	Tachycardia	Bradycardia	Variable
Salivary secretion	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/decreased	Increased/diarrhea	Variable
EEG	Normal or decreased	Early low voltage continuous delta and theta, later periodic, seizures focal 1-1,5HZ spike-wave	Early periodic pattern with isopotential phases, later isopotential
Seizures	None	Common/focal or multifocal	uncommon
Duration	<24h	2 to 14 days	Hours - weeks

There is a relationship between symptoms and anatomopathological lesions:

- Selective neuronal necrosis: spastic hemiplegia or quadriplegia with or without a cognitive disability.
- Parasagittal brain damage: proximal paresia of upper limbs with evolution to spastic proximal quadriplegia and visual and language deficits.
- Marmoratus status: extrapiramidal symptoms as dystonia and corea associated with spastic quadriplegia in 30% of the cases with a normal intellectual coefficient.

- Focal or multifocal damage: seizures
- Periventricular leucomalacia: lower limb paresis which becomes to spastic and in severe cases with intellectual and visual deficit.
- Hemorrhagic infarct: spastic hemiparesis with or without intellectual deficit.

Evolution stages of severe HIE

1. **Initial stage (6 to 12 hours of life)**: bihemispheric affectation signs with severe alteration of the alert state, periodic breathing, hypotonia, and hypoactivity. 50% of patients suffer seizures.
2. **From 12 to 24 hours of life:** apparent improvement of alert state with ocular aperture but without gaze fixation or gaze tracking and a lack of habituation to sensory stimulationcan be noticed. Neurologic damage symptoms like seizures, apnea, hypotonia and muscular weakness persist.
3. **From 24 to 72 hours of life:** this is the period with the highest risk of death. There is a great alteration of alert state (comma) with signs of brain stem affection such as the absence of photomotor reflex of the pupils, the absence of oculocephalic and oculovestibular reflexes and ataxic breathing. Intracranial hypertension could be present as well.
4. **>72 hours of life:** progressive improvement with persistent mild stupor with generalized hypotonia and muscular weakness which evolves to hypertonia and extension. There are alterations in suction, deglutition and nausea reflex because of the affectation of cranial pairs V, VII, IX, X, and XII.(15)

Systemic affectation goes along with severe HIE and it involves the following organs:

Lungs	Pulmonary hypertension, hemorrhage, and respiratory distress
Heart	Transitory myocardial ischemic, tricuspid insufficiency and contractility deficit.
Kidneys	Transitory tubular dysfunction or acute tubular necrosis
Digestive	Necrotizing enterocolitis, hemorrhagic gastritis
Liver	Hyperammonemia because of liver fail, coagulopathy and alteration of drug metabolism
Metabolic	Hypoglucemia, hypocalcemia, hypomagnesemia, inadecuated secretion of ADH
Hematology	Hemolytic anemia and intravascular disseminated coagulation.

2.5 TESTS WITH DIAGNOSTIC AND PROGNOSTIC VALUE

The events that can provoke a lack of oxygen in the newborn are produced in the time which surrounds the delivery, thus test which will have diagnostic value will be performed in this period.

First, the tests which are performed, allow checking the fetus status. It is used cardiotocographic register which shows if there are signs of non-reassuring fetal status.

Cardiotocographic Register

It measures the fetal cardiac frequency, its variability, its accelerations and decelerations and its relationship with contractions.

- **Basal cardiac frequency** is the average of fetal cardiac frequency, which is approximated to increments of 5 beats per minute and for 10 minutes. Accelerations, decelerations and variability periods are excluded.
  From 110 to 160 bpm is considered *Normal cardiac frequency* (preterm is closer 160 bpm and posterm is closer 110bpm).
  Taquicardia is higher than 160 bpm for at least 10 minutes.
  Bradycardia is lower than 110 bpm for 10 at least minutes.

- **Variability** is the oscillation of the FC signal, which corresponds to the average of the band amplitude in one minute. Fluctuations should be regular in amplitude and frequency. It is expressed in beats per minute.
  Normal variability: amplitude 5-25 bpm
  Not normal variability: it can be the absence of variability, the increment or different patterns which are explained in annex 1.

- **Accelerations** are increments of the cardiac frequency in 15 bpm of amplitude wich last from 15 seconds to less than 10 minutes.

- **Decelerations** are decreases of the cardiac frequency of 15 bpm which last 15 seconds.

- **Contractions** are registred in a bell-shaped graph with a gradual increment and a symmetrical decrease. The register only measures contraction frequency.

- The cardiotocographic register also measures **fetal activity status** such as deep sleep, active sleep and wakefulness.(Annex1) (4)

Sentinel events during the delivery can produce asphyxia in the newborn, so they have to be diagnosed as soon as possible.

Placenta abruption, uterus break, cord prolapse, and fetus-matern transfusion are causes of sentinel events and they have to be detected. Clinical manifestations, echography and cardiotocographic register help in diagnostic.

Once the newborn is born he /she has to be evaluated.

The need for reanimation considering it as a set of precedents that are performed to ensure cardiorespiratory function immediately after birth, is carried out when there are some alterations that compromise vital functions. (17)

APGAR SCORE is a vitality and adaptation evaluation method after birth. It is performed at 1 minute of life, after 5 minutes of life and after 10 minutes.

This test rates 5 parameters which are: cardiac frequency, respiratory effort, muscular tone, gestures, and skin color. Each one of these parameters has punctuation from zero to two which are added giving a result from zero to ten, being ten the best value.

Table 4 APGAR TEST (18)

	0 (Points)	1	2
Appearance	Blue or pale all over	Blue extremities, but torso pink	Pink all over
Pulse	None	< 100	≥ 100
Grimace	No response	Weak grimace when stimulated	Cries or pulls away when stimulated
Activity	None	Some flexion of arms	Arms flexed, legs resist extension
Respirations	None	Weak, irregular or gasping	Strong cry

0-3 Critically Low, 4-6 Fairly Low, 7-10 Generally Normal

Umbilical pH and acid-base balance

An umbilical pH less or equal to seven indicates that the newborn suffers from acidosis. A disturbance in acid-base balance is one of the most sensitive and earliest signs of fetal distress. It could be measured in the cord or in the fetus scalp.

An acid ph increases the likelihood of having a 50% abnormal outcome.(19)

Clinical manifestations in the newborn

The HIE is present since birth without a period free of clinical manifestations. The evolution of the course allows differentiating if the encephalopathy is prenatal (its pattern is stable) or perinatal (whose pattern is dynamic). Furthermore, temporal evolution could help to know the outcome. (6)

Clinical manifestations such as hypotony, hypoactivity, seizures or difficulties to breathe are collected and mentioned in tables 2 and 3 presented in ´´Symptoms and signs in the newborn´´. In both of the classifications, all the items have the same value to establish the severity of HIE. However, the most important item that shows nervous system affectation is the capacity to awake or maintain the alert.(7,20)

Graduation of consciousness García Álix table 5 (7,20)

Normal	**The newborn awakes spontaneously**
Blunted	The newborn awakes easily but with stimulation and maintains alert more than 6 seconds
Lethargic	The newborn awakes difficultly with disturbing stimulus and maintains the alert less than 6 seconds
Stupor	The newborn awakes difficulty with painful stimulus and comes back to sleep when the stimulus finish.
Comma	The newborn does not awake with a painful stimulus

Prognostic tests

Integrated amplitude electroencephalogram

The electrocerebral activity should be monitored in all the children with HIE. It helps to decide if the child has to be treated with hypothermia or not and its findings must be documented and classified according to base paths, sleeping and waking cycles, and paroxistic ictal activity. (3)

The aEEG is nowadays, one of the best prognosis evaluations within the first 48 hours of life. (21)

The patterns which are important to recognize in this test are those which are not normal and associated with worse outcome in neurodevelopment. Non-abnormalities or mild abnormalities predict a normal neurologic outcome in >90% of the cases and severe abnormalities predict death or disability in most the cases. The evolution of the aEEG patterns during the following 24 hours after the birth towards normal pattern (continuous background pattern with physiologic features) indicates normal neurologic outcome. However, the evolution towards abnormalities or not evolution to normal aEEG predict a poor neurologic outcome. (22)

Continuous and discontinuous patterns are considered physiologic although discontinuous patterns could be pathological too.

In figure 1 is shown an aEEG monitor with normal or continuous pattern.(23)

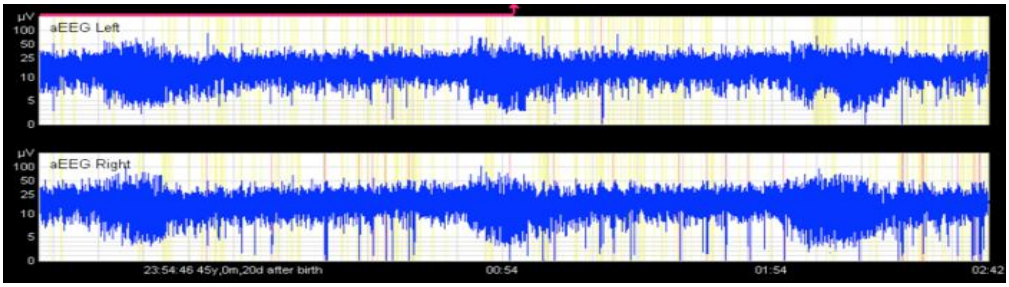


Figure 1, continuous pattern aEEG.(23)

Another normal pattern but also pathological is the discontinuous pattern that is shown in figure 2.

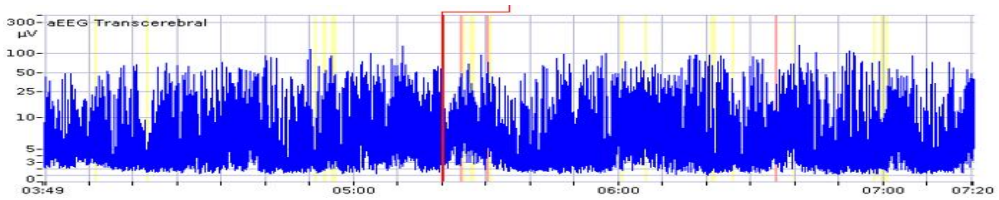


Figure 2, discontinuous pattern.(23)

Patterns such as burst-suppression, plain plotted and low voltage are pathological (figures 3,4 and 5)

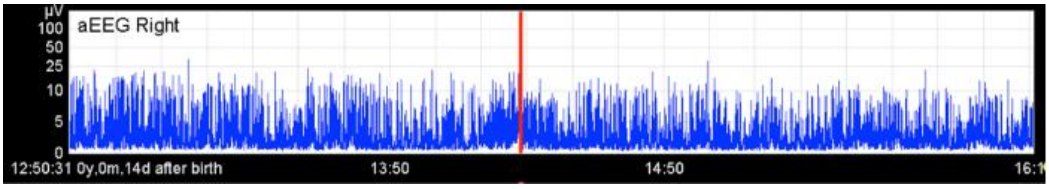


Figure3 burst-suppression.(23)

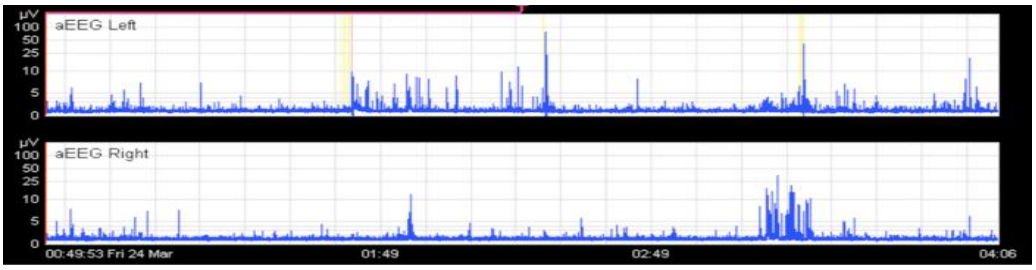


Figure 4 plain plotted(23)

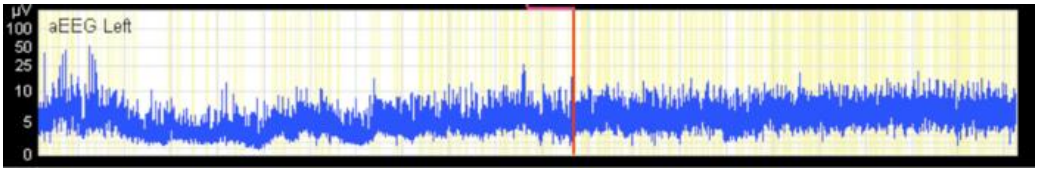


Figure 5 low voltage with the normal path. (23)

Seizures in the newborn at term has a characteristic form, with a sudden rise of the basal line. In preterm seizures could be camouflaged in a discontinuous pattern. (Figures 6 and 7). (3)

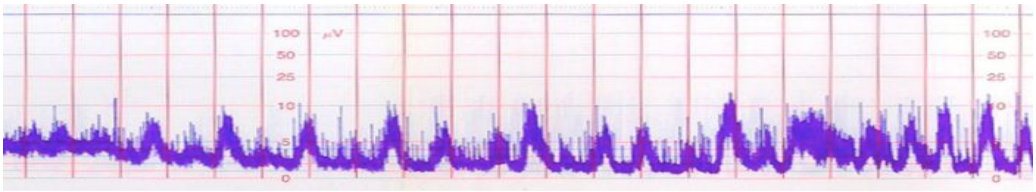


Figure 6 seizures in the newborn at term. (23)

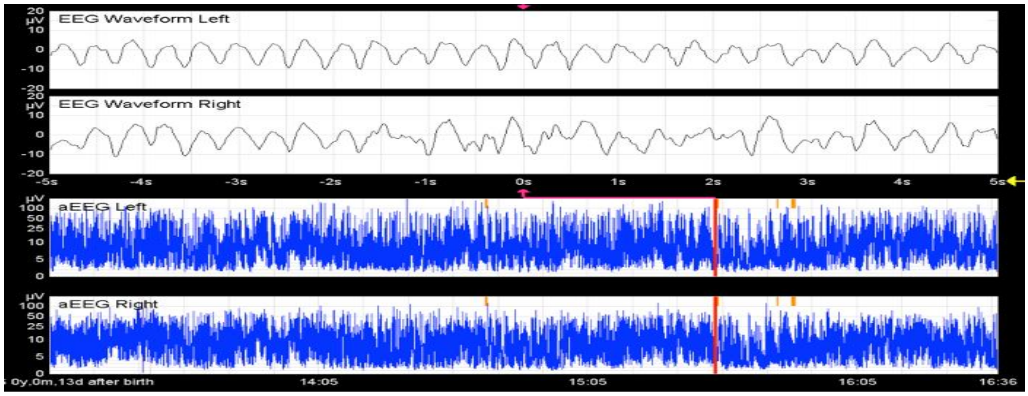


Figure 7 Seizures in the newborn preterm. (23)

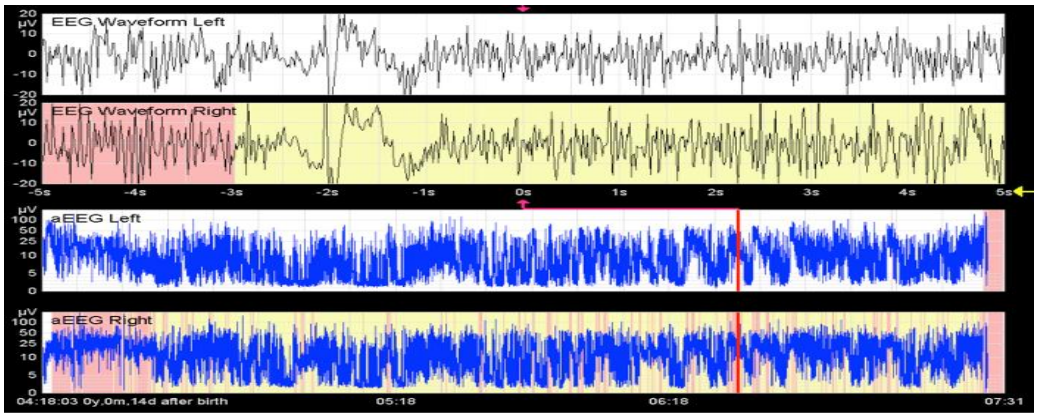


Figure 8: Stricking seizures. (23)

Standard electroencephalogram should be performed at any moment if there are clinical or electrical seizures during hypothermia or rewarming, and before discharge, if there are alterations. (3)

Cerebral Ultrasonography

This evaluation must be performed in neonatal intensive care and it allows excluding cerebral development anomalies or detecting a different pathology by which symptoms are caused.

Serial Doppler ultrasonography shows the evolution of the brain damage and measures the pulsatility index of the cerebral artery which gives prognostic information useful before hypothermia treatment.

Normal values of pulsatility are between 0,65 to 0,85 and values under 0,55 are common in neonates with severe HIE.

Abnormal values in the first six hours of life suggest hypoxic-ischemic aggression produced one or two days before delivery.(3)

Magnetic Resonance

It shows structural lesions produced by hypoxic-ischemic aggression. It is performed after hypothermia (days 3 to 5 of life because of its importance to take decisions like limitation of therapeutic effort) or during the second week of life and includes sequences in T1, T2, diffusion and spectroscopy.(3)

Brain affection in resonance can be simplified in two patterns of injury; watershed and basal ganglia/thalamic. The image depends on the severity, the timing and the type of the study.

The watershed affects the area between the major arteria supplies and deep in the sulci with edema, infarction and cortex necrosis. On MRI between days 3 to 5 it is seen as restricted perfusion areas on diffusion. Conventional T1 and T2 can be normal these days but after the eighth day the signal in T1 increases in the sulcal depths near the interhemispheric fissures. White matter can be also affected. Watershed is related to cognitive disabilities.

The second pattern of injury is basal ganglia/thalamic, which happens most commonly in acute HIE. Deep grey matter is the first structure affected because of its necessity of energy substances affecting, after that, sensorimotor cortex. It is seen as a hypertense signal in diffusion. In severe cases, it could be seen in T1 image even at an early stage. After that, the injury is better seen in T1 with increased intensity in ventrolateral nuclei of thalami and in the grey matter if it is severe. This pattern is related to cognitive and motor disabilities.

These two patterns are not pure when we are looking at resonance image because the pathological process is a continuum and it depends on how long it lasts, variability and severity of the encephalopathy giving to the image a mixture of appearances.

The absence of abnormalities in the resonance image indicates the low likelihood that a severe neurodevelopment impairment is produced.

Therapeutic hypothermia can affect the results because it modifies the course of the brain lesions but it does not change its predictive value. Resonance can be carried out on days four or five of life, after hypothermia.(24–26).

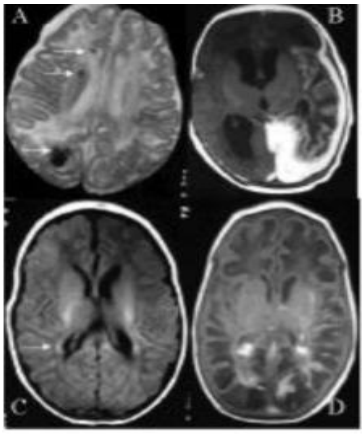


Image 1 Patterns in the resonance of perinatal asphyxia: A) Hypotense images with a hemorrhagic infarct in the parasagittal area.
B) Focal lesion of a hemorrhagic infarct in asphyxia with subdural hematoma associated. C)Leucomalacia periventricular. D) Severe edema with evolution to multicystic encephalomalacia and hemorrhagic subacute focus.(27)

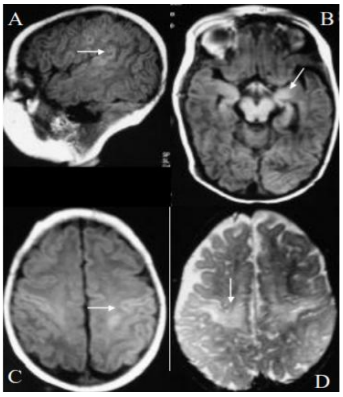


Image 2: Cortical lesion in perinatal asphyxia.
A) Cortical enhancement in the depth of the sulci.
B)Bilateral hyperintensity in hippocampus. C)Perirolandic hyperintensity. D) Perirolandic lesion at 12months (27)

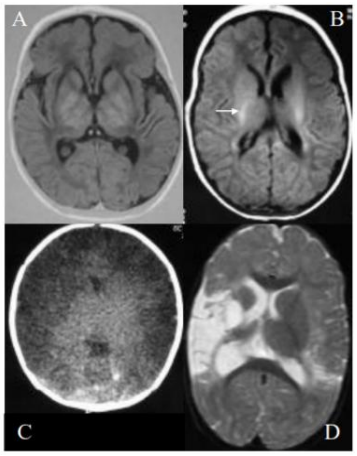


Image 3: Basal ganglia lesion in asphyxia. A) Bilateral hyperintensity of nigroestriado nuclei and thalam with lack of hyperintensity in the posterior arm of the intern capsule in T1 which seems normal in B. C) Severe edema with bihemispheric hypointensity in TAC image. D) The same patient after 12 months reveals a lesion in lenticular nuclei and thalamus with focal ischemia associated with the right middle cerebral artery and mild affectation in the other side.(27)

Biomarkers of cerebral damage

Clinical evaluation and aEEG can be affected by medication and therapeutic interventions, that's why biomarkers of damage are determined.
Biomarkers used to know the existence of cerebral damage are more or less specific proteins of the nervous system.
The mainly biomarkers in the blood or cerebrospinal fluid are specific neuronal enolase (ENE, protein S100B, the acidic fibrillar protein of the glia (PFAG), activin A, interleukin 6 (IL6) and determined in urine S100B and lactate- creatinin quotient. (3)
Specific neuronal enolase is a protein that diffuses easily to both extra cell space and cerebrospinal fluid when there is an aggression.

Protein S100B, activin A and interleukin 6 are related to the severity of the hypoxic-ischemic aggression but its prognosis is still contradictory.(7)

2.6 HANDLING AND TREATMENT

The healthcare process until therapeutic hypothermia is crucial to improve the effectiveness and to prevent the aggravation of ischemic damage.

When there is a situation where there are compatible data with perinatal hypoxia or ischemia as non-reassuring fetal status (cardiotocographic register and dystocia in the delivery) or sentinel event, it is a priority to start asistencial process of the newborn.(28,29)

At birth is important to evaluate the need for advanced reanimation, APGAR score, and umbilical pH.

The need for reanimation, APGAR equal or less than 5 at 5 minutes of life and a pH equal or less than 7 orientate to perinatal asphyxia.

Healthcare process starts in maternity ward. The following actions have to be performed.(29)

- Turn off radiant heat and monitor preductal arterial saturation of oxygen.
- Start reanimation with FiO2 21% and to modify the concentration of oxygen according to clinical manifestations.
- Avoid administrating bicarbonate or volume expanders
- Do not administrate calcium
- Take rectal temperature and avoid values less than 34 degrees and more than 36 degrees.

The newborn must be moved to neonatal intensive care with hypothermia treatment. If the hospital has not the possibility to provide this treatment, the neonate has to be

moved to a hospital with this possibility. (The transfer will be in passive hypothermia and the newborn has to be performed a glycemia, gasometry, control of blood pressure and cardiac and respiratory frequency).(29)

Things to be carried out in intensive care:

- Continue with radiant heat off
- Monitor the cardiac and respiratory frequency and to stabilize the newborn hemodynamically.
- Take the rectal temperature continuously or every 30 minutes.
- Continue, monitoring the amplitude electroencephalogram
- Monitor regional cerebral saturation of oxygen
- Monitor CO2 concentration with a capnograph
- Detect clinical manifestations of HIE (described in table3, Sarnat classification)
- Perform arterial gasometry and glycemia
- Avoid: hyperthermia, hypoglycemia, hypocapnia, hyperoxia, hypoxia, hypercapnia, hypocalcemia, hypomagnesemia and hypotension or oscillations of arterial pressure.
- Graduate the severity of HIE with Sarnat (table 3) or García Álix classification (annex 2). In Sarnat classification more than 3 items classify the grade, but if the items are equal for two grades the classification will be completed with alert state.
    - In a neonate who has suffered mild HIE it is necessary a close watch, avoiding the situations mentioned before and to perform continuous amplitude electroencephalogram during 24 hours, and ultrasonography at 72hours of life. These neonates will need a tracing in the posterior psychomotor neurodevelopment.
    - Moderate to severe affection indicates the necessity for hypothermia treatment.(29–31)

Hypothermia treatment

Hypothermia treatment improves survival and neurodevelopment of neonates who have suffered from HIE moderate to severe although the effect is more important in moderate group. It consists of decreasing neonate temperature until 33.5 degrees.(29,32)

To perform this treatment the newborn who is a candidate to receive it must comply with a series of inclusion criteria.

CRITERIA A
Infants less than six hours old and ≥34weeks of gestation and >1800grames
APGAR ≤5 in the first 5 minutes of life
Reanimation in maternity Ward during more than 10 minutes with positive pressure ventilation
pH <7 in the worst gasometry during the first 60minutes of life
Bases deficit ≥16mmol/L in the worst gasometry during the first 60 minutes of life

Neonates who comply with one of the A criteria will be evaluated neurologically through B criteria.

CRITERIA B
Signs and symptoms of HIE moderate or severe: **1- Seizures** **2- Clinical manifestations of HIE moderate or severe:** **- Alteration of conscience state (poor answer or absent to stimulation) and** **- Abnormal muscular tone (general or focal hypotony) and** **- Primitive reflexes absent or abnormals (weak suction, abnormal Moro réflex)**

With every neonate who complies A and B criteria will initiate hypothermia treatment while they are evaluated C criteria.

CRITERIA C
≥30 minutes of amplitude electroencephalogram with one of the following scenarios: **- Continous pattern base with convulsions (clinical or subclinical)** **- Continous convulsions or epileptic status** **- Alteration of the base pattern (discontinuous, burst suppression) or submit (low voltage or isoelectric)**

If the electroencephalogram is normal in the first 6 hours of life and a clinical recovery is observed, there is a great likelihood of a normal neurologic outcome and hypothermia treatment is not indicated, therefore the newborn has to be rewarmed slowly and has to be hold at 36-36,5 degrees.(29,32)

Hypothermia treatment must be started before 6 hours of life although newborns under 12 hours of life are also included. If the neonate was born in a hospital without the possibility of hypothermia treatment, the newborn has to be moved in passive hypothermia to a hospital that can offer the treatment.(29)

Do the following to all neonates treated with hypothermia:

- Monitor cardiac frequency, respiratory frequency, arterial pressure, arterial oxygen saturation, glycemia, capnograph, pulse oximetry, and cerebral oximetry.
- Rectal sondage to meausure temperatura and superficial sonda to meausure superficial temperature.
- Monitor with amplitude electroencephalogram
- Place umbilical catheters and vesical sondage
- Blood test and gasometry.
- Ventilation if it is needed
- Aspirate tracheal and oral secretions and change the position of the neonate every 6 hours because hypothermia increases secretions.(29)

During hypothermia treatment, the following objectives will be attempted:

- To maintain normal oxygenation and normocapnia (pO2 60-95 with saturation 92-94% and pCO2 40-50). Low corporal temperatures reduce metabolism and energetic consume with a less CO2 production. Hypocapnia provokes cerebral vasoconstriction, diminution of oxygen liberation from hemoglobin, neuronal excitability, diminution of seizure threshold, and cell death. In neonates whose necessity of oxygen increases by 30%, raising the temperature has to be considered. If the oxygenation fails, rewarming is necessary.(29,33)

- To maintain cardiac frequency between 90 to 100 bpm and mean blood pressure >40mmHg since hypothermia produces bradycardia and affects arterial pressure.
- To control renal function and hydroelectrolytes (sodium 135-145mEqu/L, potassium 3,5-5,5mEqu/L, calcium >7mg/dl and magnesium >1,6mg/dl)
- To maintain glycemia between 70 to 100mg/dl
- To maintain correct sedation and analgesia to avoid stress and pain
- To maintain correct coagulation since hypothermia modifies plaquettes and time of coagulation. It is necessary to correct coagulation alterations with plasma transfusion and if bleeding is produced or there is a coagulopathy, is necessary to stop hypothermia and start rewarming.
- To nourish the newborn with glucose serum because hypothermia decreases blood flux in the intestines favoring necrotizing enterocolitis.
- To treat actively every clinical or subclinical epileptic crisis.

After 72 hours from the beginning of hypothermia treatment rewarming will be performed.

Rewarming will be initiated slowly and gradual 0,4 degrees per hour and if there is some complication such as convulsions or hypotension, it will be considered to carry out a slowly rewarming (0,1-0,2 degrees per hour).

Rectal temperature will be monitored for 24hours after getting normothermia to avoid rebound hyperthermia. (29,32,33)

2.7 OUTCOME AND SEQUELS

Most children who have needed resuscitation at birth will recover without early signs of HIE and their neurodevelopment will be almost normal. (19,34)

It was believed that their neurodevelopment was normal until it was shown in large population studies that these children had an increased risk of low intellectual coefficient. (19,35)

Short term outcome in newborns who have suffered perinatal asphyxia is different depending on the severity of their HIE classified by Sarnat.

With a mild HIE,the newborn has no risk of mortality and he or she has got a risk between 6% and 24% of having a slight retard in psychomotor development.

Moderate HIE has a 3% risk of mortality and moderate or severe disability in 20 to 45% of the cases.

Severe HIE has 50% to 75% risk of mortality and neurological sequels are near to 100%.

Asphyxia is a global brain damage but it affects differently depending on the regions, because of factors as the maturity of the brain at the incident, duration of the incident

and severity. Different types of brain damage have different sequels that can associate motor, cognitive and behavioral disabilities. (36–38)

Treatment with hypothermia has increased the survival with normal intellectual coefficient and less neurological sequels but the risk of sequels is still threefold higher if there is a history of seizures.(19,39)

The following manifestations are common disabilities that are produced because of HIE.

- Dyskinetic cerebral palsy which is caused in the 80% of the cases because of intrapartum hypoxic- ischemia.
  It consists of changing the muscular tone and involuntary movements that lead to uncontrolled motion, the persistence of primitive reflexes during the infancy, normal or near-normal intellectual coefficient but difficulties in communication because of dysarthria due to bulbar muscular affection which also affects to deglutition causing the need of gastrostomy. It could be accompanied of lesions in grey matter.
  In MRI, we can see the affection of posterior putamina of lentiform nuclei, ventral nuclei of thalami, hippocampus, perirolandic cortex and white matter.(36,40)
- Spastic tetraplegic cerebral palsy is the affection of four limbs with spasticity and it is almost always associated with severe disability in the long term. It is accompanied of learning difficulties and epilepsy.
  In MRI it is seen the affection of the parasagittal area and grey matter.
- Ataxic cerebral palsy is the consequence of cerebellar ataxia and it is rarely due to hypoxic ischemia if it is isolated. However, abnormalities in the anterior lobe of cerebellar vermis are part of the spectrum of acute hypoxic-ischemic damage but not in isolation and not as a cause of ataxia cerebral palsy.
- Epilepsy is the most currently additional disability in patients with cerebral palsy and it is rare without motor disability as a result of hypoxic-ischemic damage.
- Learning disability is a consequence of deep grey matter and it is related to cerebral atrophy or hippocampus affection if we are talking about memory problems. Its manifestations are episodic memory difficulties with irritability and attention disorder but with semantic and working memory in the low range of normality or above. (36,41)
- Visual impairment caused by abnormal basal ganglia function and it is defined as poor acuity but a useful vision. It is not isolated. (40)

- Behavioral impairment schizophrenia and psychotic disorders with early-onset (7 to 13 years old) could have a relation with obstetric complications and with asphyxia because of the hippocampus affection acts as a contribution to the genetic but nowadays it is not known how this contribution is. (36,41–43)

2.8 ETHICAL ISSUES

The birth of a child who has suffered perinatal asphyxia whose outcome is poor in terms of risk of death and/or morbidity is a decision making challenge that demands a rigorous analysis of the available information.

When clinical expression and prognostic tests show a bad prognosis there is no reason to complete 72hours of hypothermia or to maintain intensive treatments. These situations involve irreversible comma between 48 to 72 hours, a permanently altered electroencephalogram and severe alterations in ultrasonography and resonance.

Limitation of therapeutic effort is a set of procedures that tries to adjust medical treatment dynamically in those cases in which medical practices could be useless to improve outcome, life quality, and benefit of the patient. Sometimes, the treatment until the certainty leads to therapeutic obstinacy that can cause damage in the patient or the family. (44,45)

The decision to limit therapeutic effort responds to two criteria:

Survival: the decision is less complex because the diagnostic and evolution will indicate the time when the limitation has to be performed. It responds to the nonmaleficence ethical principle of medicine.

Poor quality of life: it is more complex because it is an evaluation of likelihoods and the utility which involves a judgment of values. It responds to beneficence ethical principle and not everybody understands it the same way. (44)

When we approach parents who are going through this situation, it is important to look for tools to be offered as well as to supply the information needed and help them to make decisions and to get through this situation.(3)

Effective and transparent communication among professionals and parents is essential. Empathy and compression of the parent´s feelings when they visit their baby is also important. (44,46)
We should take into account that, in most cases, whenever parents express unsatisfaction in neonatal intensive care it is not because their child has not received good medical care but because parents´ needs have not been attended.(44,46)

Parents are in a difficult situation and they need us to help them to know all the resources that they could need. They could feel many strong emotions when they

watch their baby's situation such as impact, anxiety, frustration, pain, fear, incomprehension, distrust, and inability to take care of their child. Also, there are times, in which the mother has to be separated from the baby because of medical issues and this can be a difficulty to stand in reality.(3)

As professionals, giving them the tools and the information is a must. These needs are:

- Overall, adapted information, explaining carefully to them what is happening with their child, treatment steps, outcome, and every success that may occur.
- To be recognized as parents with the ability to make decisions for the good of their child and to take care of the infant.
- To know and using hospital resources as 24 hours free access to the neonatal unit, a psychologist, a social worker, mothers and fathers group, associations and foundations, and a spiritual guide if they want it.
- To feel that they are part of the care of the baby and to feel that they can take care of themselves.
- To receive information about financial support and social assitance they can apply for. (3,44)

There are patients who suffer severe damages with serious consequences for their future life or will cause the decease of the child. These patients could need the interruption of treatments which do not benefit baby´s condition.
The decision to stop the treatment will be made jointly by professionals and parents. Never make the professional take the decision alone.(3,44)

At the end of the baby´s life, we must avoid baby suffering proportionating analgesia and drugs which favour baby´s comfort. (3,44,45,47)
The decease of a child is a high impact in society and in the family so support in grief is needed.
The family can spend the final moments with their child holding the baby in their arms, taking some pictures and keeping baby´s objects as the hospital´s bracelets and clothes. (44,47,48)
Families with social exclusion risk need special attention and it is necessary to provide them with appropiate assistance. (44,45)

It is needed to remember that medical assistance includes taking care and not just curing.

 (3)

3. CEREBRAL OXIMETRY

3.1. GENERALITIES

Noninvasive cerebral oximetry uses near-infrared spectroscopy to measure oxygen saturation of regional cortical cerebral vessels. It monitors changes in cerebral metabolism reflecting the balance between oxygen aport and tissue demand. (49,50)

NIRS technology gives an indication of cerebral oxygenation and blood flux and allows detecting every acute change in cerebral hemodynamic continuously and not invasively.

Light photons are emitted near to infrared in the patient´s skin and after their dispersion on the scalp, skull, and brain tissue part of them come back to the skin because of the reflectance.(7,49–51)

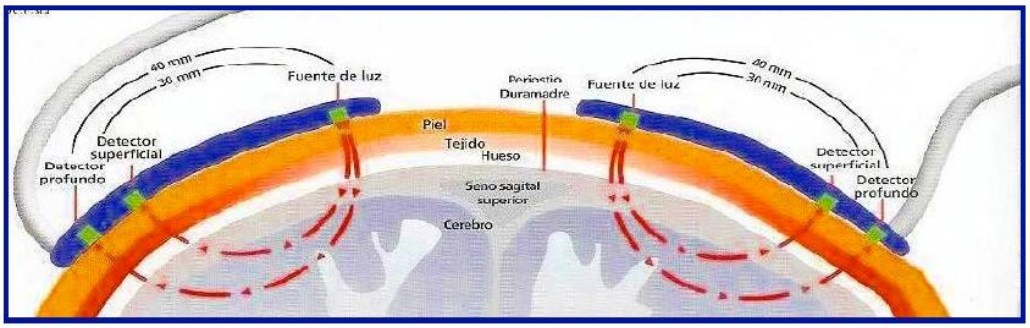


Image 4 (49)

If we measure the number of photons which return to the skin, it can be inferred the spectral absorption of the tissue and can be achieved conclusions about the average of oxygenation.

When the photons are dispersed by the tissues they are absorbed by chromophore materials producing signals characteristic in emerging light spectrum. The chromophore with the highest light absorption is the hemoglobin whose spectrum changes depending on its oxygenation.

The cerebral vascular bed is conformed by exchange vessels which are 25% arteries and 75% veins and this affects the interpretation. (7,49–52)

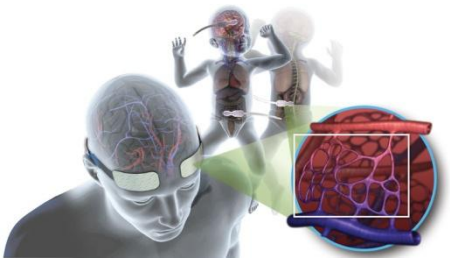


Image 5 (7)

How deep the photons can penetrate depends on the distance at which the detector is located. Two detectors are used and they are located at two different distances from

the transmitter; the nearest receives the signal of superficial tissues such as the skin, the subcutaneous tissue, and the skull. The furthest receives the signal of cerebral tissue. The difference between the two signals gives the correspondent value to the cerebral cortex under the sensors. (7,49)

3.2. INVOS DISPOSITIVE

Two sensors are colocated on both sides of the middle line and both of them have a transmitter and two detectors situated at three and four centimeters from the transmitter. The area monitored is the region perfused by middle and anterior cerebral arteries whose anatomy makes them more vulnerable to oxygen deficiencies.(49,51,53)

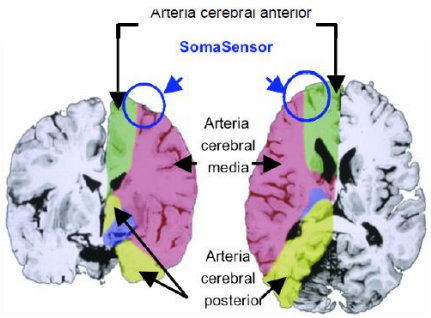


Image 6 (49)

Two light sources are emitted with different wavelengths, 730mm to deoxygenated hemoglobin and 810mm to total hemoglobin. The intensity of light that receives each detector and it becomes in en electric signal which is processed and digitalized and the values of regional saturation of oxygen in the brain appear on the screen in a range of 15% to 95%. It can also be shown the tendency of overtime on the screen. (7,50,52,54–57)

The normal range of regional cerebral oxygen saturation measured by INVOS equipment is between 55% to 85%.(7,50,52–54)

These values are achieved at 15 minutes of life and they are maintained in this range during all neonatal period.(7,52)

Image7 INVOS dispositive (7)

Less than 50% of saturation can provoke damages in cerebral tissue according to animal and humans studies. It is a risk of cognitive deterioration, damage in the frontal lobe, cerebral infarction, an extension of mechanical ventilation and the prolongation of hospital discharge. (7,52,56,58)

Cerebral consume of oxygen is higher than renal consume and because the cerebral oximetry measures the concentration in exchange vessels the values of saturation are lower than renal ones. (7,59)

It is important to know what sensor is used since neonatal sensor detections are lower than adult´s sensors and it is also important where to place them as this could bring an important difference.(7,59)

3.3. INVOS DISPOSITIVE LIMITATIONS

This dispositive such as continuous wave dispositive has limitations.

-It is considered that light dispersion through tissues is constant and the distance is the same in all the cases. However, the light changes its way depending on the structures it collides with, therefore the distance can vary as much a 20% from a newborn to another.

-The dispositive does not take into account the proportion between arterial blood and venous blood change influencing the saturation values.

-Ambient light can interfere in the measure of cerebral oximetry although the sensor is covered to minimize it.

-Skin color can also influence cerebral oximetry value; Afro-American people have lower values than Caucasian people.(7,60)

This condition that the values of the oximetry are not considered absolute but a tendency. It is important to evaluate the evolution and to control ambient interferences. This is why the variation between patients and in the same patient is important and the range of normal values to INVOS dispositive be large.

Although these limitations INVOS monitor has demonstrated having a good correlation with other variables that reflect oxygen consumption as venous saturation measured at different levels as jugular, superior cave vein, right auricle or pulmonary artery becoming in a useful tool in neonatology. (7,50,59,60)

JUSTIFICATION

JUSTIFICATION

In infants with HIE, it is important to know the severity of the brain damage because of the risk for the neonate of having disabling sequels and the risk of decease.

Nowadays, the severity of HIE is estimated from clinical classifications and tests, such as the amplitude electroencephalogram. When the severity is classified as moderate or severe, newborns can be treated with hypothermia.

The early outcome estimation of these scales and tests is still uncertain and, only magnetic resonance can provide a certain prediction of the outcome but no sooner than the third day of life, after hypothermia.

Cerebral oximetry has demonstrated to be useful to differentiate the grades of HIE severity, therefore, it is interesting to analyze if we can use the values of regional cerebral saturation of oxygen as a prognostic factor that added to all the tests and examinations performed before, can allow us to make decisions in an early way.

These medical and family decisions are very important for the newborn since they imply providing specific treatment or rather, limiting therapeutic effort and providing just comfort to the newborn and the family until the moment of the decease.

The weight of these decision relapses in parents and professionals should have as much information as it is possible to help them. Parents need to know the chances of living of their child or if heor she is having serious disabling sequels and all the consequences of their decisions-making.

If we have more evidence about the early outcome, we can advise the parents better for the needs of their baby and the best for him or her.

HYPHOTESIS AND OBJECTIVES

HYPOTHESIS

-Cerebral oximetry values are associated with the prognosis of newborns who have suffered from HIE so it can be useful to predict the early outcome.

-Cerebral oximetry pathological values are related to electroencephalographic paths which predict poor outcome.

-Cerebral oximetry values considered as pathological are associated with greater brain lesions in magnetic resonance, severe sequels and more risk of mortality.

OBJECTIVES

1) Studying if cerebral oximetry values can predict the early outcome of hypoxic-ischemic encephalopathy in neonates measured in ranges which are pathological (<55% and >90%) or normal ranges (55% to 85%).
2) Analyzing if more pathological values in cerebral oximetry are associated with those electroencephalographic paths which are related to the worst outcome, such as discontinuous, burst-suppression and convulsions.
3) Studying if more pathological values in cerebral oximetry are translated into greater brain damage in magnetic resonance and sequels risk.

MATERIAL AND METHODS

MATERIAL AND METHODS

STUDY DESIGN

This is a descriptive, observational, transversal and multicentric study designed to analyze the value of cerebral oximetry in the early outcome of HIE and the association between its pathological values with electroencephalographic pathological paths, brain damage in magnetic resonance and sequels.

STUDY VARIABLES

Main variables per objectives:

1) *To study if cerebral oximetry´s values can predict the early outcome of hypoxic-ischemic encephalopathy in neonates measured in ranges which are pathological (<55% and >90%) and normal ranges (55% to 85%).*

-Cerebral oximetry values which represent the regional saturation of oxygen in the blood circulating through exchange arterial and venous vessels and it reflects the balance between tissue´s demand and the oxygen provided.

- Normal values measured with cerebral oximetry with INVOS dispositive newborns are between 55% to 85%, these ranges are achieved at 15 minutes of life (which is related to the time when the newborn needs to get an adequate arterial oxygen saturation) and they are maintained during the neonatal period.
- Pathological ranges which are <55% and >90%. Less than 55% of cerebral oxygen saturation can produce damages in cerebral tissue. Studies in adult and pediatric patients with these ranges of cerebral saturation confirm that these patients have more risk to develop sequels, such as cognitive and motor alterations.
  More than 90% of cerebral oxygen saturation suggests that brain tissue has its cell metabolism altered because of neuronal damage and because of hypothermia treatment.(7)

-Outcome

- Good prognosis in patients with HIE is defined as the absence of any disability or developing only mild disability.
- Bad prognosis is defined as a greater risk of developing moderate to severe disability and risk of death.

2) *To analyze if more pathological values in cerebral oximetry are associated with those electroencephalographic paths which are related to the worst outcome as discontinuous, burst-suppression and convulsions.*

-**Cerebral oximetry values** (defined above)

-Electroencephalographic paths are associated with future neurodevelopment outcomes. Such patterns will be classified as being either, normal or pathological. Normal patterns (continuous or sometimes discontinuous) indicate a greater likelihood or normal psychomotor development.
The following patterns are considered pathological.

- Discontinuous pattern
- Burst- suppression pattern
- Seizures

3) *To study if more pathological values in cerebral oximetry are translated in greater brain affectation in magnetic resonance and sequels risk.*

-Cerebral oximetry values (defined above)

-Brain affection in resonance is a continuum and it depends on the duration, variability and severity of HIE and the timing we are looking at the images.
According to the presence or absence of abnormalities in resonance, there will be greater sequel or less.
Those children whose resonance does not present abnormalities or they are minimum have a low likelihood of suffering a severe neurodevelopment impairment.(24–26).

- Sequels and mortality.
Sequels are defined as the presence of one or more of the following manifestations.

- Dyskinetic cerebral palsy
- Spastic tetraplegic cerebral palsy
- Ataxic cerebral palsy
- Learning disability
- Epilepsy
- Visual impairment
- Behavioral impairment

Mortality defined as death within two weeks after birth.

Secondary variables:

- Sex: female or male
- Gestational age at birth measured in weeks.
- Acidosis defined as a pH less than 7 which is related to abnormal outcomes in 50% of cases.
- The hemodynamic shock which is the inadequate transport of oxygen because of a decrease of hemoglobin or blood flux. It will be determined with blood pressure and hemoglobin in the analysis.
- Neonatal sepsis which is the invasion and proliferation of pathogen microorganism in newborn´s blood during the first 28 days of life.

STUDY POPULATION

Inclusion criteria

- Newborns >34 weeks and >1800grames of weight who had suffered asphyxia.
- Asphyxia as a cause of HIE is defined with essential criteria or with a set of suggestive criteria that prompt a perinatal event.
- Neonates with HIE grades mild, moderate and severe following Sarnat classification.

ASPHYXIA CRITERIA

- *Essential criteria*
  1) Metabolic acidosis during delivery (pH< 7 and BD >12mmol/L
  2) Early beginning of HIE
  3) Cerebral palsy; spastic quadriplegia or dyskinetic cerebral palsy

- *Suggestive criteria*
  1) Sentinel event before or during delivery
  2) Sudden or maintained deterioration of cardiotocographic register after the sentinel event.
  3) APGAR 0 to 6 after 5minutes of life
  4) Brain damage or alteration in neuroimage

Exclusion criteria

Newborns with the one or more of the following conditions will be excluded from this study:

- Dying neonate at birth
- <1800g of weight
- Congenital syndrome
- Severe congenital malformations
- Metabolism disease
- Neuromuscular disease suspicion
- Congenital cardiopathy

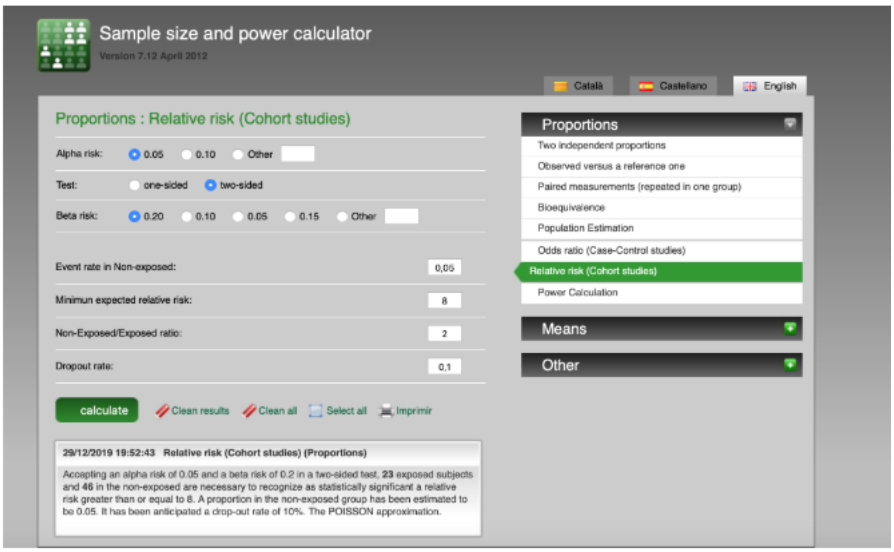
SAMPLE SELECTION

A consecutive non-probabilistic sampling will be followed in newborns with have suffered HIE and who meet inclusion criteria and none of the exclusion criteria in the hospitals that will participate in the study.
This is a multicentric study because of the need to get the sample taking into account the incidence of HIE is around 1,6 of 1000 neonates alife.

The centers which will be asked to participate in this study are:
-H. Universitari Dr. Josep Trueta, Girona.
-H. Sant Joan de Deu, Barcelona.
-H. Vall d´Hebron, Barcelona.
-H. Can Ruti, Barcelona.
-H. Parc Taulí de Sabadell, Barcelona.
-H. Joan XXIII, Tarragona.

SAMPLE SIZE

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 23 with abnormal ranges in oximetry subjects and 46 in the normal ranges of oximetry (69 in total) are necessary to be able to detect as statistically significant a relative risk of sequel or mortality greater than or equal to 8. A proportion in the normal ranges group has been estimated to be 0.05. A drop out rate of 10% has been anticipated. We have used the sample size and power calculator GRANMO.



TIME OF RECRUITMENT

HIE is an uncommon pathology, it´s incidence in newborns is 1,6 per 1000 live newborns. In each one of the abovementioned hospitals, the natality rate is around 3000 per year, therefore, 3 years of recruitment are needed to complete the sample size of 69 patients.

DATA COLLECTION

When a newborn with HIE is about to born with a cardiotocographic register let us know if the fetus is suffering giving us a little bit of time to inform the parents. Once he or she is born, he or she will be evaluated to know if he or she accomplishes the inclusion criteria and not the exclusion criteria. The baby will be examined by the neonatology team present in the maternity ward or in the operating room. If the newborn accomplishes the criteria one of the doctors of the neonatology team will explain the family the pathology of their baby and what he or she will be performed. The doctor will also explain the study which we will perform and will give them the informed consent to let us recollect the information we need and to perform the tests and the treatment if it is needed.

To monitor cerebral oxygen saturation it will be used INVOS 5100C dispositive with the neonatal sensor, hydrocolloid adhesive free of latex and PVC and it will be located in the frontal region of the head of the newborn.

The monitorization will be initiated in all the patients upon admission and it will be maintained within hypothermia treatment until at least 24 hours after rewarming or until the fourth day of life in newborns who do not need hypothermia treatment.

The values of regional cerebral saturation of oxygen will be collected and registered in nursery control table each hour. Furthermore, the values of renal saturation of oxygen will be registered too.

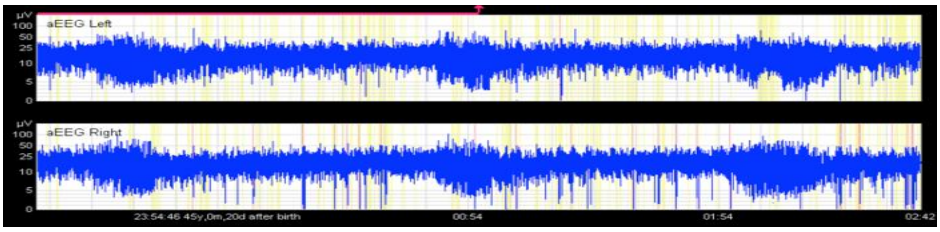
Oximetry data will be classified in three intervals: less than 55%, 55 to 90%, and more than 90%. Complete registers from 0 to 96 hours and hourly intervals will be analyzed. The hourly intervals will be: 0-6h/6-12h/12-24h/24-36h/36-48h/48-72h/72-96h.

In nursery controls table, vital constants such as temperature, respiratory frequency, cardiac frequency, blood pressures (systolic, diastolic and mean pressures), and aEEG patterns will be registered. The results of the gasometries will be written down too.

Temperature, gasometry results (pH, pCO_2, pO_2, lactic acid, bicarbonate, and base deficit) and pressures will be used to analyze if they influence cerebral saturation of oxygen being able to affect the study. Because of the characteristics of the gasometry, this test will be performed once per day.

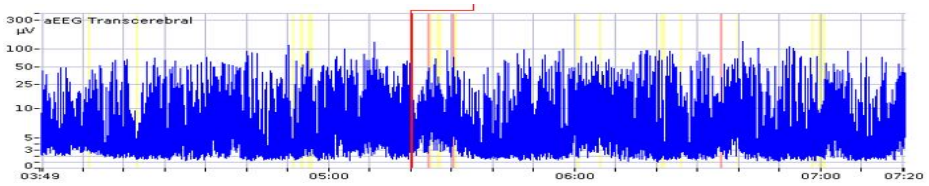
Those aEEG patterns used in the study will be:

- Continous: continuous activity with a minimum amplitude of 5-10µV and maxim of 10-25µV.



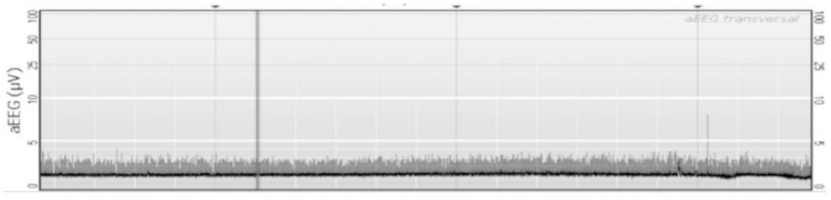
(23)

- Discontinuous: discontinuous path with minimum variable amplitude, but less than 5µ, and maximum more than 10µV.



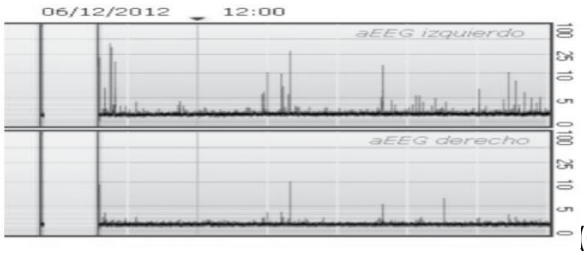
(23)

- Low voltage :<5µV with amplitude smaller than 10µV



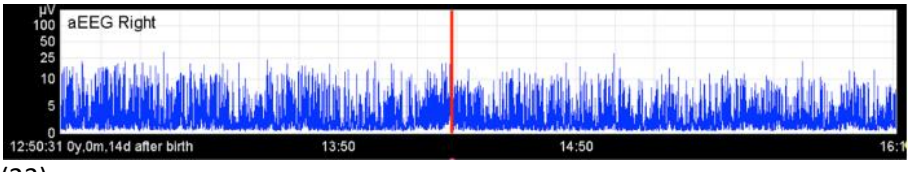
(61)

- Plain or inactive: isoelectric path lower than 5µV



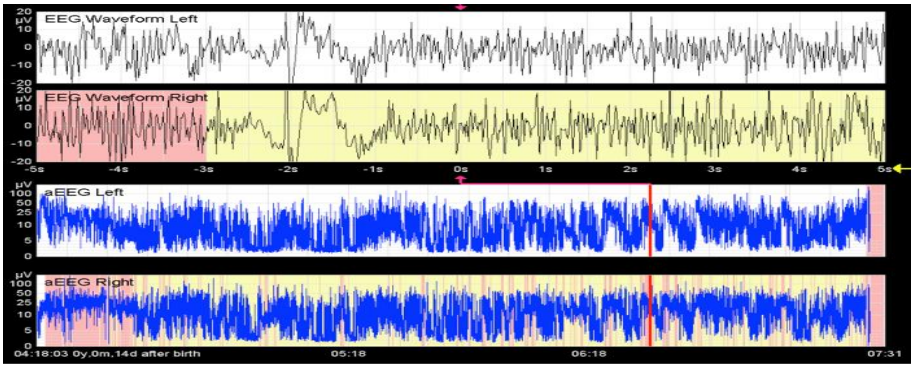
(61)

- Burst-suppression: discontinuous path with minimum amplitude without variability between 0-1µV and bursts with more than 25µV.(62)



(23)

- Seizures are shown like an elevation in the minimum amplitude and a simultaneous elevation in the maximum amplitude.(62)



(23)

The magnetic resonance will be performed after rewarming or within the first week of life and data will be collected in a descriptive way according to the information performed by the radiologist (this will be performed once). They will be classified in:

- Without abnormalities or minimum
- With abnormalities
- Extensive lesions

Sequels are the most difficult to analyze in this study because most of them do not define themselves until neuropsychomotor development is not completed. Although they can be predicted according to the area affected in the resonance.

There is a relationship between symptoms and anatomopathological lesions:

- Selective neuronal necrosis: spastic hemiplegia or quadriplegia with or without a cognitive disability.
- Parasagittal brain damage: proximal paresia of upper limbs with evolution to spastic proximal quadriplegia and visual and language deficits.
- Marmoratus status: extrapiramidal symptoms as dystonia and corea associated with spastic quadriplegia in 30% of the cases with a normal intellectual coefficient.
- Focal or multifocal damage: seizures
- Periventricular leucomalacia: lower limb paresis which becomes to spastic and in severe cases with an intellectual and visual deficit.
- Hemorrhagic infarct: spastic hemiparesis with or without an intellectual deficit.

Mortality will be analyzed based on whether or not it occurs within the first two weeks of life.

WORK PLAN

This study will be performed in six different hospitals so the data collection has to be done the same way in all of them.

-Phase 1 of the study: we will create a table with all the items which have to be recorded every hour (pH, hemodynamic variables, temperature, sepsis, oximetry values, aEEG patterns, resonance patterns, and early sequels). An example is added in annex 4. We will meet with the heads of doctors of neonatal UCI and the heads nurses of neonatal units from the hospitals which are going to participate to train them.

-Phase 2 will consist of patients´ recruitment and data collection because sampling is non-probabilistic and consecutive. Patients who accomplish inclusion criteria will be selected and their data will be collected. Because of the low incidence of HIE this phase will last three years to get the sample size.

-Phase 3 of the project will be the analysis of the data collected. It will have a descriptive part and an analytic part with a bivariable and multivariant study such as it is described in the analysis statistic part of this protocol.

-Phase 4 will be the interpretation of the results and the dissemination of the research findings.

SCHEDULE

Activity	People involved	November and December 2020	The year 2021	The year 2022	The year 2023	The year 2024
Stage 1: Project preparation and coordination						
Creation of the data collection table and meetings	Head of the project, general coordination, heads of nurses and doctors	X				
Stage 2: Fieldwork						
Patients and data recruitment	Doctors and nurses of neonatology service		X	X	X	
Stage 3: Analysis						
Analysis of the data	Statistical consultant and head of the project with general coordination					X
Stage 4: Results and findings dissemination						
Interpretation of the results and research findings dissemination	Statistical consultant and general coordination					X

STATISTICAL ANALYSIS

DESCRIPTIVE STATISTIC

The description of the categoric variables will be done in percentages or in absolute frequency depending on the variable which is studied.

The description of quantitative variables, when they follow a normal distribution, will be done with the average ±1 standard deviation. When they do not follow a normal distribution, they will be done with the median and the maximum and minimum of the values.

ANALYSIS STATISTIC

-Bivariable study

Main aim

We compare the dichotomic categoric variables (oximetry values and outcome) through the Chi2 test. When the application assumptions are not met, statistical signification is estimated with the Fisher test.

Second and Third aim

The average of oximetry values according to the electroencephalogram of amplitude pattern and resonance pattern will be compared with the ANOVA test.

We will assume a statistical signification level of 5%: $p < 0,05$.

-Multivariant study

Main aim

Binary logistic regression will be used. To build a predictive logistic regression model we will select those relevant variables with greater theorical justification.

Second and Third aim

A lineal general model will be used to analyze the difference of oximetry averages according to electroencephalogram of amplitude patterns and resonance patterns, adjusting with covariables (sex, gestational age, acidosis, hemodynamic shock and sepsis).

ETHICAL ASPECTS

The study must have a good medical practice following the Declaration of Helsinki, of the ethical principles for medical research involving human subjects, collected in the 64ª General Assembly, Fortaleza, Brasil, October 2013.

Although all the tests performed in this study are part of the habitual clinical practice, it is necessary that parents sign the informed consent and to inform them we are going to analyze the data that we collect and why we are going to collect and analyze them.

We will work respecting the data confidentiality according to the Organic Law 3/2018 of 5 December on Protection of Personal Data.

An Ethics Review conducted by the Clinical Research Ethics Committee of the Josep Trueta Hospital of this protocol will be performed before starting.

LIMITATIONS OF THIS STUDY

This is an observational, descriptive, transversal study and as a limitation of these types of studies we can not establish a causal relationship, we only will know if there is an association between the variables.

The limitations of this study will be those derived from the limitations of the oximetry device explained in cerebral oximetry apart.

Although these limitations INVOS monitor has demonstrated having a good correlation with other variables that reflect oxygen consumption as venous saturation measured at different levels as jugular, superior cave vein, right auricle or pulmonary artery becoming in a useful tool in neonatology. (7,50,59,60)

When we talk about sequels we have to take into account that we cannot evaluate them exactly until the child has finished his or her development, so we will have to analyze them according to resonance lesions and the symptoms expressed early.

BUDGET

Material resources

No extra money will be needed for the realization of the study because cerebral oximetry is part of clinical practice nowadays.

Human resources

It is needed to contract a statistic group of people to analyze the data collected according to the analysis mentioned in the section of the statistical analysis of this protocol. It will cost 50€ per person and hour. If they are three people and they will work 30 hours in total it will cost 1500€.

IMPACT IN HEALTH CARE

Cerebral oximetry is a noninvasive test, painless and easy to monitor and to perform. If it is related to the prognosis of the newborn, we will know earlier and with more certainty, than nowadays the severity of the brain damage.

This will help us as doctors and the tutors to make decisions about how to treat the newborn and if it is necessary to propose the limitation of the therapeutic effort.

Knowing the outcome in an early way in these cases is important because we will orientate the family with more certainty about where we are and where are we going to, what the baby can suffer, what cares he or she will need and what is his or her life expectancy.

If we know the outcome early in some of the cases, it could help us to make the decision of limiting the therapeutic effort avoiding therapeutic fierceness which does not bring any benefit to the patient.

ANNEXES

ANNEX 1: THE CARDIOTOCOGRAOHIC REGISTER

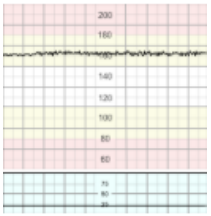
It measures the fetal cardiac frequency, its variability, its accelerations and decelerations and its relation with contractions. Sentinel events during the delivery can produce asphyxia in the newborn, so they have to be diagnosed as soon as possible.

Placenta abruption, uterus break, cord prolapse, and fetus-matern transfusion are causes of sentinel events and they have to be detected. Clinical manifestations, echography and cardiotocographic register help in diagnostic.

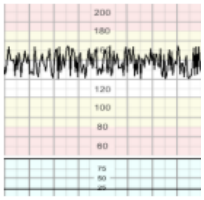
As it was explained in the paragraph ``Tests with diagnostic and prognostic value´´, cardiotocographic register evaluates fetal cardiac frequency, its accelerations and decelerations, its variability and its relationship with contractions.

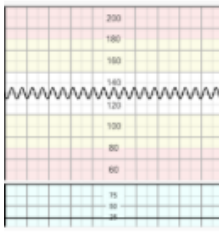
-Variability is the oscillation of the FC signal, which corresponds to the average of the band amplitude in one minute. Fluctuations should be regulars in amplitude and frequency. It is expressed in beats per minute.

Normal variability: amplitude 5-25bpm
Not normal variability: it can be the absence of variability, the increment or different patterns.

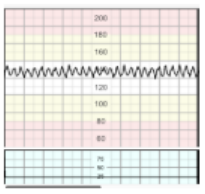

Variabilidad reducida

1. Reduced variability: the amplitude is less than 5bpm for more than 50 minutes in the basal line, or more than three minutes during decelerations.
2. Silent variability: the amplitude is indetectable with or without decelerations.
3. Saltatory pattern: the amplitude is more than 25bpm for at least 30 minutes. It is not understood the physiopathology but it could be related to recurrent decelerations when the hypoxia or the acidosis occurs quickly. It is believed that it is caused by the autonomic instability of the fetus.

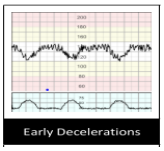

Patrón saltatorio

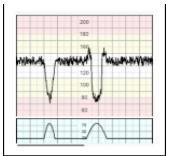

Patrón sinusoidal

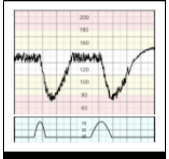
4. Sinusoidal pattern: it is a regular undulation with an amplitude of 5-15bpm and a frequency of 3-5 cycles in a minute. It lasts more than 30 minutes and requires the absence of accelerations. It is related to fetal anemia, fetal to fetal transfusion, previous vasa break, infections, hypoxia, cardiac malformations, hydrocephalus, and gastroschisis.
5. Pseudosinusoidal pattern: it is similar then sinusoidal but with more angulation and lasts more than 30 minutes. It has been shown when previous vasa break occurs and when the fetus makes pacifier movements.

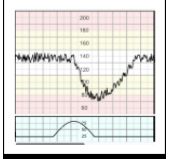

Pseudo-sinusoidal

-Decelerations are descendants of the cardiac frequency of 15bpm with a duration of 15 seconds. They are an answer to diminish fetal cardiac output when there is a mechanic or hypoxic stress.


Early Decelerations


Variable Decelerations


Late Decelerations


Prolonged Deceleration

1. Early decelerations: they diminish the basal line and come back to its place gradually. They coincide with the contractions specularly and they are not translated like hypoxia.
2. Variable decelerations: They have V form and show a quick fall with a basal recuperation. These decelerations are common in delivery and they do not indicate hypoxia unless they have U form with reduced variability.
3. Late decelerations: the recuperation is very gradual and there is an increment or diminish of the variability inside of deceleration. These decelerations indicate an answer to fetal hypoxia mediated by chemoreceptors.
4. Prolongated decelerations: those whose duration is more than 3 minutes. It is likely that they are mediated by chemoreceptors and they indicate hypoxia. If they surpass 5 minutes with cardiac frequency maintained of 80 bpm and reduced variability inside the deceleration they are associated with hypoxia or acidosis and an urgent actuation is required.

-Contractions are registred in bell-shaped with a gradual increment and symmetric descend. The register just measures the frequency of contractions.

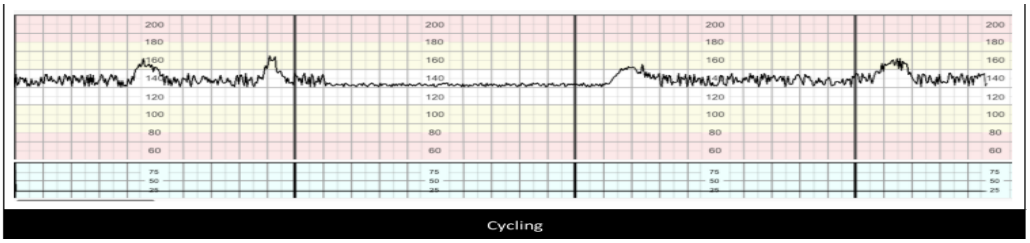
1. Taquisystolia is an excessive frequency of contractions and it is defined as the presence of more than 5 contractions in ten minutes in two successive periods of ten minutes or doing the average in thirty minutes.
2. Hyperstimulation is the exaggerate answer to uterine stimulants presenting and increment of frequency, strength, and tone of the contractions prolonged in time more than 2 minutes. This can cause changes in fetal cardiac frequency.

Fetal activity states

It refers to:

1. Fetal quiescency reflects deep sleep without ocular movements; it lasts 50 minutes and is associated with a stable cardiac frequency without accelerations and with the variability in the low limit of normality.
2. Active sleep is the common state (with ocular movements) and there are some accelerations and conserved variability.
3. Awake: there are multiple accelerations so frequent that it would be difficult to determinate the cardiac frequency.

The alternation of different states of behavior (cycling) is a sign of a good neurological state and the absence of hypoxia or acidosis. The transition between the different states is more evident after 32/34 weeks of pregnancy because of the nervous system maturation. (4)



ANNEX 2: GARCÍA ÁLIX CLASSIFICATION OF HIE SEVERITY

Table 6: García Álix scoring system for hypoxic-ischemic encephalopathy(63)

Grade	Clinical items	Clinical signs	aEEG items	aEEG recording[d]
Mild	Alertness Muscular tone Motor responses Reactivity Clinical seizures	Normal Altered: hypotonia (usually) or hypertonia, Normal or slightly decreased Normal or hiperexcitability: increased myotatic reflexes, tremor and/or myoclonus None	Background amplitude or pattern SWC Electrographic Seizures	Normal or moderately abnormal. Present or absent Absent
Moderate	Alertness Muscular tone Motor responses Reactivity Clinical seizures	Lethargy or moderate stupor[a,b] Altered: usually hypotonia Greatly decreased, normal quality Decreased tendon reflexes, weak primitive reflexes Present or absent	Background amplitude or pattern SWC Electrographic Seizures	Moderately or severely abnormal Absent Present or absent
Severe	Alertness Muscular tone Motor responses Reactivity Clinical seizures	Severe stupor or coma[b,c] Altered: hypotonia (usually) or hypertonia Absent or stereotyped. Primary reflexes absent Present or absent Frequent signs of brain stem dysfunction	Background amplitude or pattern SWC Electrographic Seizures	Severely abnormal Absent Present or absent

SWC, sleep-wake cycle.
[a] Lethargy; difficulty to wake up to noxious stimuli and when awake up maintains the alertness a few seconds (≤6″).
[b] Stupor: wake up with great difficulty to noxious stimuli and infant quickly falls asleep.
[c] Coma; failure to wake up upon nociceptive stimuli.
[d] The worst aEEG segment of 30 min to 1 h in length before clinical evaluation. Grading: **Normal trace**: normal continuous voltage pattern (upper margin >10 μV and lower margin >5 μV); **Moderately abnormal trace**: discontinuous pattern (upper margin >10 μV and lower margin ≤5 μV). **Severely abnormal trace**: burst suppression pattern (upper margin <10 μV and lower margin <5 μV; often accompanied by bursts of high voltage activity), continuous low voltage (upper margin <10 μV and lower margin <5 μV), or isoelectric pattern (upper and lower margin <5 μV, with no burst of activity).

ANNEX 3: WHAT HAPPENS NEXT? SOCIAL AND INCLUSION WORK

Disability is a word which englobes deficiencies, activity limitations, and participation restrictions. Deficiencies are problems that affect a structure or body function, activity limitations are difficulties to perform actions and restriction of participation are problems to participate in vital situations. Thus, disability is a phenomenon which shows an interaction between human characteristics and the characteristics of the society where the person lives in. (64)

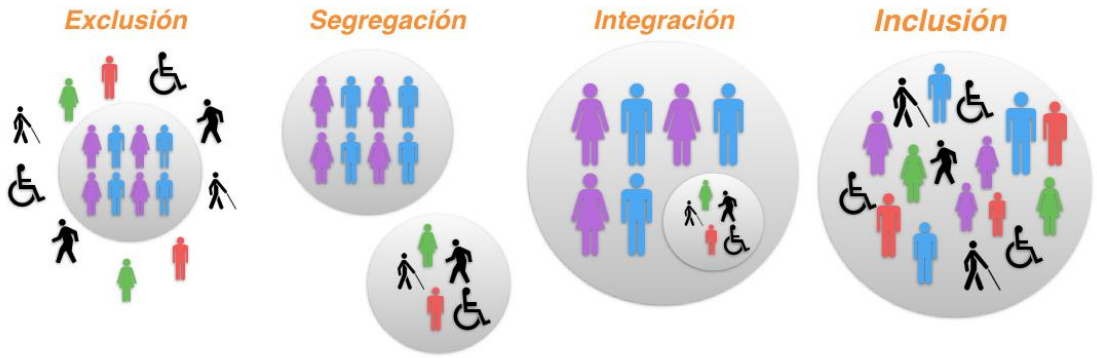
Children who have a disability have exactly the same rights such as any child if they get the opportunity to prosper like the other children, those with disabilities will have the potential to have a full life and to contribute to the social, economic and cultural vitality of their communities. However, this is difficult for these children because even if they share the same unfavorable conditions, these children have additional problems because of their own impediments and the impediments that society imposes to them. (65)

In many countries, the most common answer to disability is institutionalization, abandonment or lack of care. The origin of these answers is the negative notion of disability, dependency, and differences caused by ignorance. Children with a disability afront different ways of exclusion depending on the place where they live, culture o social class.(65)

The Convention about the rights of people with disabilities requires that all the children without exception are full members of their families, communities, and societies. This implies to leave behind the traditional notions of saving the child and change it for measures to eliminate physical, cultural, communication and mobility barriers that avoid the compliment of childhood rights. (65)

Víctor, un niño de 13 años con parálisis cerebral, se divierte en el agua, en el Brasil. © Andre Castro/2012

Underestimating the potential of people with disabilities is one of the factors which attempts the most against their inclusion and the equality of opportunities. Negative attitudes happen in all the statements of the society, from professionals, politicians to children´s mates and also themselves who underestimate their own abilities. (65)



The European Union defines inclusion like a process that assures that people at risk of poverty and social exclusion have the same opportunities and resources to participate completely in the economic, cultural, and social life enjoying a standard of living considered normal in the society where they live in. (65)

Nowadays, inclusion is not a reality, there is still a long way to go to get the equity and it is necessary to work in the following areas:

- To ratify and launch the Convention about the Rights of People with Disability and Children´s rights.
- To fight against discrimination and improving the awareness about disability in the general population, politicians, and people who proportionate services to the children.
- To eliminate the barriers to facilitate access and to promote the participation of children with disabilities with children without them.
- To finish with the institutionalization of the children with the promotion and support to the families.
- To support the families with economical aids, so they can proportionate the necessary attention to their children.
- To coordinate the services in all the sectors to help the problems that the children and their families have to face.
- To make them as independent as they could be and to engage them in the decisions they are affected by.
- To promote research programs that generate necessary results to orientate the plan and the administration of resources. (65)

EXAMPLES OF INCLUSION

ASPAYM Castilla y León is an entity whose hallmark is working to improve specifically life conditions of people with disabilities and spinal cord injuries. It was founded in 1992 to answer the needs of the patients of the ``Hospital Nacional de Parapléjicos´´ who did not have a service that attended them.

It has been growing over the years with the aim of promoting the autonomy, equality of opportunities and rights and the quality of life of the people with disabilities to assure them a full social and work inclusion.

Twenty-three years ago ASPAYM started a summer camp where disabilities are not an exclusion element, there are children with and without disabilities and all of them live, participate and play together.

Each August for 12 days ludic-educative activities are carried out and they are used to demonstrate that inclusion is possible. In this summer camp, all the activities are adapted so all the children can play them no matter if they have or not a disability and which disability they have.

The experience is extremely enriching to the children and to the leaders. Both of them learn values, get to know each other, make new friends, enjoy participating in the activities and grow personally. (66,67)

Comienza el XXII Campamento ASPAYM para más de 120 niños con y sin discapacidad

2 Agosto 2019 · Nota de Prensa / Federación Nacional ASPAYM / Real Patronato sobre Discapacidad

Este XXII Campamento ASPAYM se está desarrollando desde el 31 de julio al 11 de agosto en Cubillos del Sil, León y este año participán más de 120 personas, 61 de las cuales disfrutarán de la modalidad de campamento con pernocta, además es un espacio para disfrutar del ocio inclusivo y de mucha diversión con actividades como karting y piscina.

ANNEX 4: DATA COLLECTION TABLE

Name of the child:

Sex:

Gestational age:

	0h	1h	2h	3h	4h
Temperature					
Respiratory frequency					
Cardiac frequency					
Blood pressures					
Gasometry results(pH, pCO2, pO2, lactic acid)					
aEEG patterns					
Resonance patterns					
Early sequels					
Cerebral oximetry values					
Renal oximetry values					

ANNEX 5: INFORMED CONSENT

Intensive care unit informed consent:

Dades del/la pacient
Cognoms:
Nom:
NHC:

Consentiment informat

Nom del procediment:

Procediments derivats de l'Ingrés al Servei de Cures Intensives Neonatals i Pediàtriques.

Descripció del procediment:

El seu fill/a ingressa en la Unitat de Cures intensives Neonatals i Pediàtriques perquè pateix una malaltia greu, que posa en perill la seva vida, i necessita un tractament i/o vigilància especial.

Riscos generals:

Poden ser necessàries mesures o tècniques que denominem de "suport vital", que no estan lliures de riscos que vostè ha de conèixer. En el cas concret del seu fill/a li explicarem quines d'aquestes actuacions seran utilitzades i per quin motiu, sempre que la urgència ho permeti.

Riscos específics:

Aquest riscos són variables en freqüència i gravetat depenent de la tècnica i del propi pacient, però els més freqüents són:

-Els derivats de la col·locació de catèters en venes i artèries que poden donar lloc a complicacions com hemorràgies, coàguls o infecció.

-Intubació i ús de respiradors, utilitzats per ajudar a substituir la pròpia respiració, també poden tenir efectes no desitjats com infeccions pulmonars, fugida d'aire per trencament del pulmó, obturacions o lesions de la tràquea.

-Reaccions adverses, fonamentalment a medicaments, per reacció al·lèrgica o efectes secundaris.

-Toracocentesis: punció de l'espai pleural per fins diagnòstics i extracció d'aire o líquid amb fins terapèutics. Pot tenir efectes no desitjats com fugida d'aire per punció del pulmó, fugida d'aire sota la pell, hemorràgia pulmonar, lesió de vasos intercostals o lesió de les vísceres abdominals.

-Pericardiocentesis: tractament del tamponament cardíac i anàlisi del líquid extret per fins diagnòstics. Pot tenir efectes no desitjats com lesió del miocardi, punció d'una artèria coronària, arítmies, lesió del pulmó o lesió de vísceres abdominals.

Les persones que cuiden al seu fill/a coneixen aquestes possibilitats i estan atents a la seva possible aparició per combatre-les, cosa que generalment transcorre amb èxit. Tot i que els efectes secundaris poden agreujar la situació del pacient, els possibles beneficis d'aquestes mesures o tècniques superen àmpliament els riscos que comporten, és per aquest motiu que només es solen utilitzar en pacients greus.

Riscos personals:

-
-
-
-

.....pare/mare/tutor de.....
expressa que ha estat informat pel Dr/a..... del motiu pel que el meu fill/a ingressa a la Unitat de Cures intensives Neonatals i Pediàtriques, de les tècniques que poden ser necessàries aplicar-li i dels riscos que poden derivar-se de les mateixes. Comprenc el contingut d'aquest document, he rebut la informació suplementària sol·licitada i accepto les mesures necessàries. En qualsevol moment de l'evolució de la malaltia del meu fill/a podré reconsiderar aquesta decisió.

A Girona, a ..... de .....de 20.....

Signatura i DNI de/la pacient o responsable legal. Signatura del metge que informa i número de col·legiat

La oximetría cerebral como un factor predictor de pronóstico temprano en neonatos con encefalopatía hipóxico isquémica.

Declaración de los tutores:

Yo padre/madre/tutor……con DNI/pasaporte……

de ……(nombre del niño o niña) he sido informado por el

profesional de la salud …… con número de colegiado……

de la finalidad e implicaciones del estudio además de la recogida de datos y su procesamiento y de los procedimientos realizados.

Soy consciente de que los datos obtenidos durante el estudio tienen como objetivo la investigación científica y que la cesión de estos datos es realizada de manera voluntaria y de que el estudio puede ser abandonado en cualquier momento sin ninguna repercusión en la atención sanitaria posterior.

He sido informado/a que puedo solicitar la eliminación de mis datos personales y se me ha permitido realizar todas las preguntas que he considerado convenientes.

Estoy conforme con la cesión de los datos para este estudio:

Firma del/ de los tutor/a/es: Firma del médico:

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BIBLIOGRAPHY

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