Postresuscitative Management of Asphyxiated Term/Preterm Infant

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In spite of successful resuscitation of an asphyxiated infant, hypoxic-ischemic encephalopathy (HIE) develops in the setting of perinatal asphyxia, which is a multiorgan system disease. Previously it was reported that involvement of one or more organs occurred in 82% of the infants; the central nervous system (CNS) was most frequently involved (72%). Severe CNS injury always occurred with involvement of other organs. Renal involvement occurred in 42%, pulmonary in 26%, cardiac in 29% and gastrointestinal in 29% of the infants (1).

Postresuscitative management of the asphyxiated infant can be divided into two categories. The first one is the general supportive care in which clinical management is directed at maintenance of adequate ventilation, cerebrovascular perfusion and adequate blood glucose levels. This therapeutic approach is necessary for the organs to regain their baseline functions. The second one is neuroprotective therapy, which should be planned according to the phase of postasphyxial injury.

General supportive care of asphyxiated infant:
Physical examination:

Physical examination of the asphyxiated infant is important for evaluation and predicting outcome. Level of consciousness (LOC), respiratory pattern, brain stem function and motor exam are correlated with the severity of asphyxial insult (2). It is better to evaluate these features periodically because they can change by time. Sarnat & Sarnat created a scoring system to evaluate the degree of asphyxia (3). (Table 1)

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(It was presented at the 2nd World Congress of Perinatal Medicine for Developing Countries, Antalya-TURKEY, 2002)

Monitoring the infant:

Assessment of the newborn's oxygen status includes evaluation of cyanosis, pulse-oximeter monitoring and blood acid-base assessment. With careful oxygen monitoring, significant periods of hyperoxia and desaturations can be avoided.

Capillary refill, color, metabolic acidosis, and heart rate can assess peripheral perfusion. Arterial blood pressure monitoring can be obtained intermittently with a non-invasive doppler device or continuously with an indwelling catheter. Acute episodes of severe hypotension during resuscitation can be managed by giving 10 cc/kg of volume over 10-15 minutes as fresh frozen plasma (FFP) or normal saline (4). In the majority of preterm infants, especially during the immediate postnatal period, hypotension is primarily caused by abnormal peripheral vasoregulation and/or myocardial dysfunction and not by absolute hypovolemia (5). For this reason aggressive volume overload can be harmful. Volume support should be limited to 10-20 ml/kg isotonic saline and if hypotension persists, early initiation of dopamine is required. Both dexamethasone and hydrocortisone in preterm infants improved hypotension, which was resistant to volume load and vasopressors (6,7). Sudden increase in blood pressure lead to capillary disruption and intracranial hemorrhage.

Elevated levels of plasma CO_2 have two effects on the central nervous system. First, increased serum CO_2 concentrations will increase tissue CO_2 levels and worsen intracellular acidosis. Second, elevated levels of CO_2 cause vasodilatation, which increase the risk for hemorrhage. Hypocarbia should be avoided as well. Decreased serum CO_2 causes vasoconstriction that worsens the cerebral blood flow (8). Transcutaneous devices can be as sensitive as 82% and specific as 94% in detecting hypocarbia and 90% and 94% for hypercarbia, respectively (9).

Table 1. Clinical Features of Hypoxic-ischemic Encephalopathy

Stage 1	Stage 2	Stage 3
Hyperalert	Lethargic or obtunded	Stuporous, responds to strong stimuli only
Normal muscle tone	Mild hypotonia	Flaccid
Weak suck	Weak or absent suck	Intermittent decebration
Low threshold Moro	Weak Moro	Absent suck
Mydriasis	Miosis	Absent Moro
No seizures	Focal or multifocal seizures	Poor pupillary light response

As a summary the aim of monitoring is to maintain adequate oxygenation and perfusion with normalization of blood pressure, and avoidance from hypercarbia and hypocarbia. Management of the infant can be individualized according to the priority of the involved organs.

Cardiovascular

Hypotension, tachycardia, poor perfusion, decreased pulses and congestive heart failure may follow severe perinatal asphyxia (10). These signs are often associated with respiratory distress. These cardiovascular effects have been referred to as hypoxic myocardiopathy or cardiogenic shock. Electrocardiogram shows myocardial ischemia and echocardiogram shows reduced contractility, and provide information about pulmonary hypertension.

Early and adequate ventilation with correction of hypoxemia, acidosis and hypoglycemia are essential. Management of cardiac injury includes the use of inotropic agents to increase myocardial contractility and cardiac output. The combination of low dose dopamine with dobutamine is an effective treatment for cardiac failure secondary to asphyxia (5,11). Hunt and Osborn (12) concluded that current data about the use of dopamine for the prevention of mortality or improvement long-term neurodevelopmental outcome in term newborn infants with suspected perinatal asphyxia was insufficient. Epinephrine should be avoided if possible because of resultant significant vasoconstriction that can worsen peripheral perfusion and contribute to metabolic acidosis. It was stated that persistently low cardiac output predicts high mortality in newborns with cardiogenic shock (13). A child with abnormal rhythms reflects the loss of central control of heart rate and carries a bad prognosis.

Pulmonary

These neonates are at risk for meconium aspiration syndrome, respiratory distress syndrome, persistent pulmonary hypertension (PPHN), pulmonary hemorrhage and pulmonary edema (14). Pulmonary involvement exhibits a wide spectrum of clinical picture changing from minimal oxygen requirement to persistent pulmonary hypertension. Hypoxia induces pulmonary vasoconstriction and pulmonary vascular resistance increases. Intrapulmonary shunts as well as right-to-left shunting across ductus arteriosus occurs (15). Echocardiogram features of the PPHN are tricuspid regurgitation, increased right ventricle pressure and right-to-left shunting. If the conventional treatment fails, PPHN should be treated with NO and ECMO (16). Alveolar lining damage and increased alveolar permeability leads to plasma and red cell effusion and fibrin deposition. As a result surfactant production is decreased. It is defined as Shock Lung (8). Treatment approach is supportive with oxygen supplementation, adequate ventilation. The role of Surfactant is controversial (17-19).

With shock lung, pulmonary edema can progressively worsen in the presence of left heart failure with subsequent increase in pulmonary capillary pressure resulting in disruption of the vessels into the alveolar space. Pulmonary hemorrhage is the worse event of the asphyxiated lung. Management includes increasing peak end-expiratory pressure in an attempt to tamponade the hemorrhage, limiting deep endotracheal suctioning and correcting homeostasis abnormalities (8).

Renal

Renal involvement occurred in 42% of the infants and presents as oliguria and azotemia (1). The cause of acute renal failure in newborn is attributed to asphyxia in 53.4% of the cases (20). The reason can be either pre-renal due to fluid restriction or inadequate blood volume or renal because of direct effect of asphyxia causing acute tubular necrosis. Elevated urine retinol binding protein and myoglobinuria, decreased urinary output, early rise in creatinine are features of renal failure (21). Studies have shown that asphyxiated newborns who develop renal failure are at greater risk for long-term neurologic sequelae and a worse

overall prognosis (22). Early predictors of renal failure are urinary NAG and beta-2 nicroglobulin and their concentrations were correlated with the severity of perinatal asphyxia (21). Luciano et al (23) indicated that decreased Doppler renal flow systolic velocity observed in asphyxiated neonates on the first day of life is a useful predictive index for subsequent development of acute renal failure with 100% sensitivity and 63.6% specificity. Treatment is supportive. IV fluid and dopaminergic doses of dopamine (2-3 microgram/kg/min). are administered to improve renal blood flow. Dialysis may be required (24).

Gastrointestinal

The significantly asphyxiated neonate is at risk for bowel ischemia and necrotizing enterocolitis (NEC). Clinical signs and symptoms to alert the physician the infant may be developing NEC are feeding intolerance, abdominal distension, abdominal erythema, bloody stools. The onset of NEC usually occurs once enteral nutrition has begun. Therefore enteral feeds are delayed by several days to a week from the initial injury to assure recovery of the intestines. Feedings may be initiated with a volume of 10-20 cc/kg/day and may be increased as tolerated.

Asphyxia may cause significant hepatic damage. Hepatic failure usually manifests itself with hypoglycemia and decreased clotting factors leading to bleeding and increase in liver enzymes especially SGPT (25). Cholestasis is also present in approximately 10% of asphyxiated infants (26). With liver injury albumin production can be impaired resulting in intravascular dehydration and edema. Progressive peripheral edema, decreased renal perfusion with poor urinary output, increased heart rate, hypernatremia, increase in BUN develops. Administration of a colloid like 5% albumin or FFP at 10 cc/kg may improve the intravascular status if vascular integrity is not disrupted from asphyxia. If albumin is <2 grams/dl, 25% albumin with a volume of 4 cc/kg/day can be administered until levels are normalized. But, if there is considerable capillary leak the cycle can only be broken when vascular stability returns.

Hematologic

Asphyxia reduces the platelet production, compromises platelet function (27,28). Therapy is to maintain platelet count>80000 during the initial 24-48 hours after birth. As the patient stabilizes lower platelet counts (20-30 thousand) can be better tolerated.

Asphyxia causes activation and consumption of coagulation factors. In addition to the direct effect of asphyxia on the clotting cascade, liver dysfunction results in decreased production of clotting factors, resulting in worsening coagulopathy (8,29).

In the presence of PT/PTT, thrombocytopenia, and low fibrinogen, administration of corrective blood products is recommended to maintain hemostasis. FFP (10cc/kg) is used to correct PT/PTT abnormalities and cryoprecipitate (1/2-1 phresis) can be used if fibrinogen level is low.

Polycythemia is not an uncommon finding in the asphyxiated neonate. The high hematocrit may be a reflection of the hypoxic environment of the fetus. Treatment of partial exchange transfusion should be initiated in a symptomatic infant to reduce the risk of injury from hyperviscosity syndrome.

In contrast to polycytemia, an affected infant will experience anemia due to bone marrow suppression secondary to asphyxia or an acute blood loss may exacerbate the anemia. Clinically, anemia will present with hypoxemia, tachycardia and acidosis. It is advised to maintain hematocrit above 40% for adequate oxygen delivery. If the delivery is traumatic a bed side sonography will help to rule out intracranial bleeding.

Metabolic

Hypocalcemia and hypoglycemia are common laboratory findings in asphyxia. Both can be easily corrected through intravascular administration of glucose or calcium. Current approach is to maintain glucose between 70-120 mg/dl (8).

Intrinsic thermoregulation of an aspyhxiated newborn can be disrupted, especially when brain stem injury has occurred or with subdural hemorrhage. Temperature instability lead to suspicion that the patient is septic resulting in a workup to rule out infection.

Central Nervous System and Neuroprotective therapy

Treatment of perinatal hypoxic damage remains a cocktail of different mixtures of interventions aimed at reducing selective neuronal necrosis (apoptosis) or infarction of cerebral tissue. Brain-oriented therapy includes pharmacologic and nonpharmocologic interventions. Drugs currently under investigation to prevent severe brain damage include inhibitors of oxygen free radical generation and free radical scavengers, antagonists of excitatory amino acids, calcium channel blockers and nitric oxide synthase inhibitors. There is strong

experimental evidence that local cerebral hypothermia (head or whole body cooling) started before postischemic seizures has a neuroprotective effect, reducing neuronal damage.

Hypothermia

Mild hypothermia is defined as a reduction in core temperature of 1-3°C, moderate as 4-6°C, severe as 8-10°C and profound as 15-20°C (30). Hypothermia is a promising method for neuroprotection because its action is against all the adverse events when applied immediately after the asphyxictic insult. Hypothermia reduces the rate of oxygen-requiring enzymatic reactions and cerebral oxygen consumption, slows the fall of PCr/Pi and confers a protective effect on the brain after ATP exhaustion. Additional experimental evidence suggests that hypothermia suppresses cytotoxic excitatory amino acid accumulation, inhibits nitric oxide synthase activity, decreases interleukin-1? levels, decreases the releases of other cytotoxic cytokins by microglial/glial cells, and suppresses free radical activity, and delayed cell death by apoptosis (30,31).

The efficacy of hypothermia is dependent on a number of factors; timing of initiation of cooling, its duration and the depth of cooling attained. The main controversy between the two modes of hypothermia is whether or not selective hypothermia can effectively cool the deeper brain structures to render the same level of protection that has been demonstrated in animal models of hypothermia. It was suggested that selective head cooling also has the same effect as whole body cooling

(32). Recently Shankaran, et al (33) reported that whole-body hypothermia for neonatal encephalopathy with a commercially available cooling system (Blanketrol II Hyperthermia-Hypothermia system). The pilot study in term infants with encephalopathy using this cooling system demonstrate feasibility of initiating whole-body hypothermia at<6 hours of age to a constant esophageal temperature (34.5°C) using servo control. Potential adverse events of hypothermia are increased blood viscosity, mild metabolic acidosis, cardiac arrhythmias, decreased oxygen availability, dysfunction of cellular immunity, coagulation abnormalities and platelet dysfunction, intracellular shift of potassium and choreic syndrome(34).

There is general aggreement that in hypoxic-ischemic injury of the brain, a cascade of biochemical events that evolves over hours to several days happen. Critical issue seems to be the timing in treatment. Charles Palmer (35)in his lecture about neurobiology of perinatal asphyxia described four phases after hypoxic-ischemic insult and treatment strategies were planned according to these phases of recovery (Table II). The interval between the end of hypoxic insult and first 8 hours is defined as latent phase. The first few hours of the latent phase is the reperfusion phase. In the phase of reperfusion-first 4 hours, there is a return of oxygenated blood to previously ischemic brain. Free radicals are generated, activated neutrophils adhere to vascular endothelial cells. In this stage it is important to prevent delayed postischemic hypoperfusion. Reducing the oxygen and glucose requirements of the brain would be helpful. The

Table 2. Current Management and Future Therapies of Hypoxic Ischemic Injury

Reperfusion phase of recovery (0-4 hours)	Latent phase (0-8 hours)	Phase of secondary energy failure (8-48 hours)
Avoid hyperoxemia, hyperviscosity, maintain normal blood pressure, C02, and glucose level	Specific inhibitors of NO	Specific inhibitors of NO for Nitric oxide/peroxynitrite
Free radical scavengers; Allopurinol, ascorbic acid, deferoxamine, Vit E	Calcium channel blockers (nimodipine)	For apoptosis: caspase inhibitors, growth factors
Antineutrophile, anticytokine agents (pentoxifylline)	Excitatory amino acid antagonists, glutamate release inhibitors (lubeluzole, lamotrigine)	Excitatory amino acid antagonists, glutamate release inhibitors (lubeluzole, lamotrigine)
Rescue hypothermia	Prolonged rescue hypothermia	Phenobarbital for seizures (40mg/kg before seizures?)
Ibuprofen for hypoperfusion (no reflow)	Calpain inhibitors for Proteases	

use of free radical scavengers, e.g. allopurinol, vitamin E could be beneficial. Magnesium sulphate has vasodilator, antioxidant, and anticytokine effects, but its potential benefit and safety are controversial (36). In this stage experimental therapies include free radical scavengers, antineutrophil and anticytokin agents (35,37).

In Latent Phase, which is characterized clinically by absence of seizures (pre seizures) and reduction in early cytotoxic edema there is a relative neurophysiological suppression. However biochemical events occurring in the parenchyma and microvessels contribute to injury. Hypoxia-ischemia results in depletion of ATP and the reduction of resting membrane potentials in neurons and glia (primary energy failure). Increased excitatory amino acids, intracellular accumulation of calcium, dysfunction of calcium-binding proteins, activation of nitric oxide synthesis, formation of peroxynitrite, production of free radicals all contribute to neuronal damage. In the phase of secondary energy failure phase (8-48h after reperfusion) coincides with the onset of cytotoxic edema and seizures. Seizures begin at about 7 hrs after reperfusion and peak at about 28hrs. At the same time there is an accumulation of excitotoxins, increased production of nitric oxide, and a fall in brain electrical activity (35).

Apoptosis and delayed cell death

Very severe hypoxic ischemic insults can cause necrosis with destruction of cellular membranes due to total mitochondrial failure. Less severe injury can trigger apoptosis. Caspase family of 'cell death enzymes' is activated in the initiation and execution of apoptosis. Inhibition of apoptosis will take place in the treatment of HIE. The over expression of bcl-2 using herpes simplex viral vectors has shown to limit neuronal death when administered prior or following focal cerebral ischemia (38). Combinations of antiexitotoxic and antiapoptotic therapies are promising for the prevention of further damage.

The recovery interval beyond 3 days can be regarded as the late phase of recovery.

Treatment of complications:
Seizures

It is important to recognize and treat seizures as early as possible. Seizures can increase CNS metabolic demand, cause the release of excitatory amino acids, lead to fluctuations in systemic arterial pressure and may cause hypoxia and hypercapnia. Phenobarbital is the drug of choice. It is usually continued until the EEG is normal and there are no clinical seizures for>2 months. The benefit of prophylactic therapy remains controversial. In a randomized control trial prophylactic barbiturate thiopental therapy did not effect the neurologic outcomes and mortality rate of the infants and seizure activity was 75% in both groups. Evans and Levene (40)reviewed 5 studies which met the criteria they proposed and concluded that prophylactic use of anticonvulsant therapy had no benefit on preventing severe neurodevelopmental disability or death. Recently Hall et al. (41)conducted a randomized, controlled, prospective study in term newborn infants with severe perinatal asphyxia. Phenobarbital therapy (40mg/kg before seizure) was associated with 27% reduction of neonatal seizures and newborns who received phenobarbital had a significant improved outcome at three-year follow-up.

Cerebral edema

Brain swelling is not the primary event in HIE and usually occurs after the first or second day of life in association with cerebral necrosis in full-term infants. Lupton et al (42) examined 32 asphyxiated term newborns and only 7 had severely elevated pressures that reached maximum levels at 36-72 hours of age. Levene et al (43) investigated the effects of mannitol in infants with increased ICP, they concluded that ICP decreased and cerebral perfusion improved but other studies do not support their data. The main strategy is to prevent fluid overload. Current data do not support routine use of steroids and mannitol.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may complicate the care of patients with severe HIE. This syndrome is due to the decreased excretion of free water and its consequences; therefore it should be treated with careful fluid restriction SIADH is characterized by hyponatremia, low serum osmolality and high urinary osmolality with continued excretion of sodium, in spite of fluid overload with bulging fontanel.

As a conclusion, supportive treatment is the basic approach to prevent from further neuronal damage. For this reason maintaining adequate ventilation, adequate cerebrovascular perfusion and adequate blood glucose levels is essential. However hypoxic-ischemic injury of the brain is a complex event that during the phases of recovery,

cerebral damage still continues. Rescue hypothermia and various pharmacologic agents are in clinical use for neuroprotection and newer ones will be added in the future.

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