Post-resuscitation management of asphyxiated neonates

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Abstract for asphyxia

Perinatal asphyxia is one of the common causes of neonatal mortality. Data from National Neonatal Perinatal database suggests that perinatal asphyxia contributes to almost 20% of neonatal deaths in India. Failure to initiate or sustain respiration after birth has been defined as criteria for the diagnosis of asphyxia by WHO. Perinatal asphyxia results in hypoxic injury to various organs including kidneys, lungs and liver but the most serious effects are seen on the central nervous system. Levene's classification is a useful clinical tool for grading the severity of hypoxic ischemic encephalopathy. Good supportive care is essential in the first 48 hours after asphyxia to prevent ongoing brain injury in the penumbra region. Strict monitoring and prompt correction is needed for common problems including temperature maintenance, blood sugars, blood pressure and oxygenation. Phenobarbitone is the drug of choice for the treatment of convulsions.

Post-resuscitation management of asphyxiated neonates

According to latest estimates by World Health Organization (WHO), approximately 4 million babies die each year before they reach the age of one month[1]. Ninety-eight percent of these neonatal deaths take place in the developing countries. Perinatal asphyxia and birth injuries together contribute to almost 29% of these deaths[1]. Most of the births in developing countries occur at home, usually attended by untrained birth attendants. Failure to initiate and sustain breathing immediately after delivery has been associated with hypoxic-ischemic injury to the central nervous system (CNS) and the clinical manifestations of this injury have been termed as Hypoxic Ischemic Encephalopathy (HIE). HIE is of concern in an asphyxiated neonate because it can lead to serious long-term neuro-motor sequelae among survivors.

Definition

There is no consensus on the definition of birth asphyxia. It is probably better to use the term perinatal asphyxia since some asphyxial events may have their origin in the perinatal period. WHO[2] has defined perinatal asphyxia as a "failure to initiate and sustain breathing at birth" The National Neonatal Perinatal Database (NNPD), 2000 used a similar definition for perinatal asphyxia[3]. It defined moderate asphyxia as slow gasping breathing or an Apgar score of 4-6 at 1 minute of age. Severe asphyxia was defined as no breathing or an Apgar score of 0-3 at 1 minute of age. Definitions based on Apgar scores may be useful as it can be used for formulating guidelines for post-asphyxial treatment of neonates. Apgar scores are also useful for predicting long term outcome in infants with perinatal asphyxia[4,5].

Indian data

According to NNPD 2000[3] data collected from 17 tertiary neonatal intensive care units in India, Apgar scores <7 at 1 minute (includes moderate and severe asphyxia) were documented in 9% of all intramural deliveries[2]. 2.5% babies continues to have Apgar scores <7 at 5 minutes of age. Bag and mask ventilation was used in 4.5% infants and less than 1% infants needed cardiac compressions and/ or medications for resuscitation at birth. Perinatal asphyxia was responsible for 20% of all neonatal deaths. Manifestations of HIE were seen in approximately 1.5% of all babies. Perinatal asphyxia was the commonest cause of still-births accounting for one-third of all such cases.

Systemic consequences of asphyxia

Perinatal asphyxia may result in adverse effects on all major body systems. Many of these complications are potentially fatal. In term infants with asphyxia, renal, CNS, cardiac and lung dysfunction occur in 50%, 28%, 25% and 25% cases, respectively[6]. The extent of organ system dysfunction determines the early outcome of an asphyxiated neonate (Table 2).

Hypoxic ischemic encephalopathy (HIE) refers to the CNS dysfunction associated with perinatal asphyxia. HIE is of foremost concern in an asphyxiated neonate because of its potential to cause serious long-term neuromotor sequelae among survivors. A detailed classification of HIE in term neonates was proposed by Sarnat and Sarnat[7]. A simple and practical classification of HIE by severity of manifestations provided by Levene is recommended for routine use (Table 2)[8].

Evolution of HIE changes

Hypoxic-ischemic brain damage is a gradually evolving process, which begins during the insult and extends beyond the resuscitation period. Although the initial brain injury is related to hypoxia and ischemia, subsequent reperfusion and generation of free radicals contributes to ongoing injury. The initial hypoxic-ischemic injury results in an area of infarction. The immediate area surrounding this area is termed as penumbra. The penumbra continues to show adverse changes in the form of neuronal necrosis or apoptosis (programmed cell death) even after the hypoxic insult is over. It is possible that these post-hypoxic changes in the penumbra area may be amenable to therapeutic interventions. Good supportive therapy is essential for the first 48 hours of post-asphyxial period to reduce neuronal injury in the penumbra area. The extent of penumbra and the

duration for which these adverse changes continue is variable. This phase may also provide a therapeutic window for newer modes of therapy in asphyxiated neonates.

MANAGEMENT OF A NEONATE WITH PERINATAL ASPHYXIA

Initial management (Fig. 1)

Management of each and every baby needs to be individualized. Given below are broad guidelines.

1. Transfer the baby to special care newborn unit.

A baby who fails to initiate and sustain respiration at birth is at risk of hypoxic brain injury and needs regular monitoring. Infants with moderate asphyxia (Apgar score 4-6 at 1 minute of age) may be transferred to the mother. However, these infants should also be monitored frequently in the first 48-72 hours for features suggestive of HIE. Infants with severe asphyxia (Apgar score 0-3 at 1 minute or need for prolonged bag and mask ventilation >5 minutes) should be transferred to a special care newborn unit for observation and treatment.

2. Maintain temperature

Place the baby under the radiant warmer after drying the baby. Maintain normal temperature of the baby. It is during these early minutes after birth that the chances of hypothermia are highest. Hypothermia imposes additional stress to the baby by increasing metabolic needs in the face of hypoxia-ischemia. This may lead to acidosis, myocardial depression, hypotension, bleeding tendency and pulmonary hemorrhage etc.

3. Check vital signs

Immediate clinical assessment should be made by recording respiration, heart rate, blood pressure, capillary refill time, temperature and oxygen saturation. Urine output monitoring should be done.

4. Start intravenous fluids (in severely affected babies)

All babies with Apgar scores <4 at 1 minute or <7 at 5minutes of age should be started on intravenous fluids. It is customary to give about two-thirds of the maintenance fluid due to the possibility of syndrome of inappropriate ADH secretion (SIADH).

5. Check blood sugar, hematocrit and blood gases.

Check blood sugar (to detect hypoglycemia or hyperglycemia), hematocrit (to detect anemia and polycythemia) and blood gases (to detect metabolic acidosis, hypoxia, hyperoxia and respiratory failure). Hyperoxia, hypocarbia and hyperglycemia are equally detrimental to an injured brain and emphasis should be given to maintaining all parameters in the normal range for the first 48-72 hours.

6. Consider infusion of volume expander

If the capillary refill time is more than 3 seconds or if there is metabolic acidosis, volume expansion with normal saline (or Ringer's lactate) 10 ml/kg over 5-10 min should be instituted. This may be repeated, if required. One should remember that decrease in vascular tone results in relative hypovolemia (preload) in babies with asphyxia. *Attention to perfusion is the single most important component of therapy of asphyxiated neonates at this stage.*

7. Miscellaneous: Vitamin K (I mg IM) should be administered to all infants with perinatal asphyxia. A stomach wash should be performed if there was meconium staining.

Subsequent management

1. Continue monitoring

Monitoring of vital parameters referred to above must be continued. Accurate record of urine output is a must. Blood gases should be checked as often as required. In addition, periodic evaluation of blood chemistry should be done: blood sugar (2, 6, 12, 24, 48 and 72 hours of age), hematocrit (once a day for the first few days) and serum sodium, potassium and calcium (once a day).

A special effort needs to be made for monitoring the neurological status of the baby. Assessment of sensorium, tone, seizures, autonomic disturbance and reflexes should be made every 4-6 hours. Hypotonia in HIE is typically differential in term babies, especially in the early stages of HIE. It affects upper limbs more than lower limbs and involves proximal musculature more than the distal musculature. Thus, scarf sign becomes readily abnormal. Flexors of neck become weak and poor traction response is seen. Seizures may be subtle in character and therefore, a close observation is required to document them. Based on the findings, HIE is classified as mild, moderate and severe using Levene's classification (Table 2).

2. Special investigations

EEG: EEG does not help in the routine management of most cases of HIE. Its use lies in prognostication to some extent. Burst suppression pattern, low voltage or iso-electric EEG indicates poor outcome.

Cranial ultrasound (US): Cranial ultrasound is not good for detecting changes of HIE in the term babies. Hypoechoic areas are seen only in very severe cases (having large areas

of infraction). In preterm babies, however, cranial ultrasound is able to detect periventricular leukomalacia and intraventricular-periventricular hemorrhage.

Computed tomography (CT): CT scan in the acute stage of HIE in term babies many show generalized low attenuation of brain parenchyma.

In general, EEG, CT and US does not help a great deal in the acute management of the baby. Their utility is essentially for prognostication.

3. Treatment (Fig. 2)

a) Maintain oxygenation and ventilation: Babies with respiratory failure require oxygen and assisted ventilation. Some babies would already be on oxygen and bag and mask (or endotracheal tube) ventilation when transferred from the labor room. Oxygenation in those babies who have adequate spontaneous breathing can be achieved in the oxygen hood. But if there is apnea, or spontaneous respiration is inadequate or there is continuing hypoxia or hypercarbia, assisted ventilation is indicated. pH should be maintained above 7.30. The target PaO_2 is 80-100 torr in term babies and 60-80 torr in preterm infants. Pulse oximeter saturation values are maintained in the 90-95% range in term babies and 90-93% in the preterm infants. The target $PaCO_2$ value is 40-45 torr.

b) Maintain adequate perfusion: Ensuring normal perfusion is of critical importance in management. The markers of normal perfusion are normal blood pressure, capillary refill time of less than 3 seconds, normal urine output, and absence of metabolic acidosis. The BP should be maintained in the upper normal range. In sick babies, arterial line is placed for guiding management of blood pressure. This is achieved by judicious use of volume expanders and vasopressors:

c) Volume expansion: Use saline, Ringer's lactate and blood to maintain intravascular volume. In sick neonates, confirm central venous pressure (CVP) by placing an umbilical venous line.

d) Vasopressors: Dopamine and dobutamine are the drugs of choice. Begin with dopamine 3-5 microgram/kg/min. Increase the dose in a stepwise fashion. At about 10 microgram/kg/min dose, if the perfusion is still poor, dobutamine should be added in a dose of 5 microgram/kg/min. The usual maximum dose of each drug is 20 microgram/kg/min.

e) Maintain normal blood glucose: Both hypoglycemia and hyperglycemia are indesirable. Glucose is the substrate for brain and its requirements go up in HIE. Hence, it must be made available. But hyperglycemia can precipitate hyperosmolality and aggravate lactic acidosis. Hence, the dictum is to maintain blood sugar above 60 mg/dl, but not exceeding 100 mg/dl.

f) Maintain normal calcium level: Calcium should be provided in a maintenance dose of 4 ml/kg/day (of 10% calcium gluconate) for 1-2 days. This may be given as a continuous infusion or as 1:1 diluted boluses, slowly under cardiac monitoring. The aim is to maintain serum calcium concentration in the normal range.

g) Maintain normal hematocrit: Anemia should be corrected and hemotocrit should be maintained >40% in ventilated neonates. It is also equally important to treat polycythemia. Polycythemia causes hyperviscosity with adverse cardiopulmonary consequences. It is therefore recommended that if the venous hematocrit in a baby is above 65%, it should be brought down to 55% by partial exchange transfusion using normal saline.

h) Treat seizures: The anticonvulsant of choice for controlling seizures is phenobarbitone. The initial dose is 20 mg/kg, intravenously slowly over 20 minutes. If there is no response, two additional doses of 10 mg/kg can be given every 15 minutes. The maximum loading lose is thus 40 mg/kg. The rate of infusion of phenobarbitone should not exceed 1 mg/kg/min and preferably an infusion pump should be used to deliver the drug. If convulsions are still uncontrolled, phenytoin sodium should be added in a dose of 20 mg/kg intravenously slowly over 20 minutes. Maintenance therapy of both phenobarbitone and phenytoin is started 12 hours later in a dose of 5 mg/kg/day in a single dose. Generally, one or both of these anticonvulsants are effective. Occasional, short-lasting, mild seizures not interfering with cardiopulmonary status may be left alone. For intractable seizures Clonazepam, Midazolam, Paraldehyde, and Valproate may be tried. Diazepam is generally avoided in neonates. ***Always look and treat for other specific etiology of seizures (hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia), which may co-exist.***

Newer modes of therapy

Corticosteroids have no role on the treatment of HIE. Likewise, the current evidence does not support the use of mannitol in the management of HIE.

Some interest has been generated in the protective role of prophylactic phenobarbitone in newborns with perinatal asphyxia. A dose of 40 mg/kg administered prophylactically was associated with a better neuro-developmental outcome at 3 years of age[9]. However another study using 10 mg/kg in a similar fashion has reported an immediate adverse

outcome with the use of phenobarbitone[10]. Recommendation for use of prophylactic phenobarbitone still awaits further studies.

A large number of drugs are under investigations for neuro-protection in HIE. These need to be used in the early period of hypoxic ischemic injury[11,12]. They act by causing blockade of free radical generation (allopurinol, oxypurinol), scavenging of oxidants (superoxide dismutase, glutathione, N-acetyl cysteine and alpha tocopherol), calcium channel blockade (flunarizine, nimodipine), blockage of NMDA receptors (magnesium, MK801, dextromethorphan) and blockage of inflammatory mediators (phospholipase A_2, indomethcin). One promising modality on the horizon is cerebral hypothermia[13]. Mild reductions in temperature of the body as a whole or of the head (brain) has been shown to minimize the effects of hypoxic ischemic encephalopathy in experimental animals and is under investigation in multi-centre trials on babies. *It may be noted that none of the modalities mentioned in this section are ready for routine use as yet.*

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Fig 1: Summary of *initial management* of asphyxiated neonates

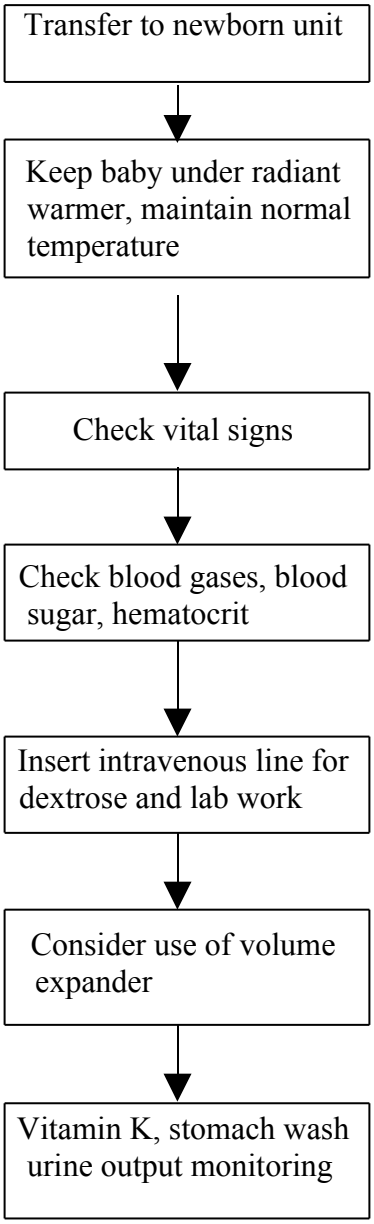

Fig. 2: Summary of *subsequent management* of asphyxiated neonates

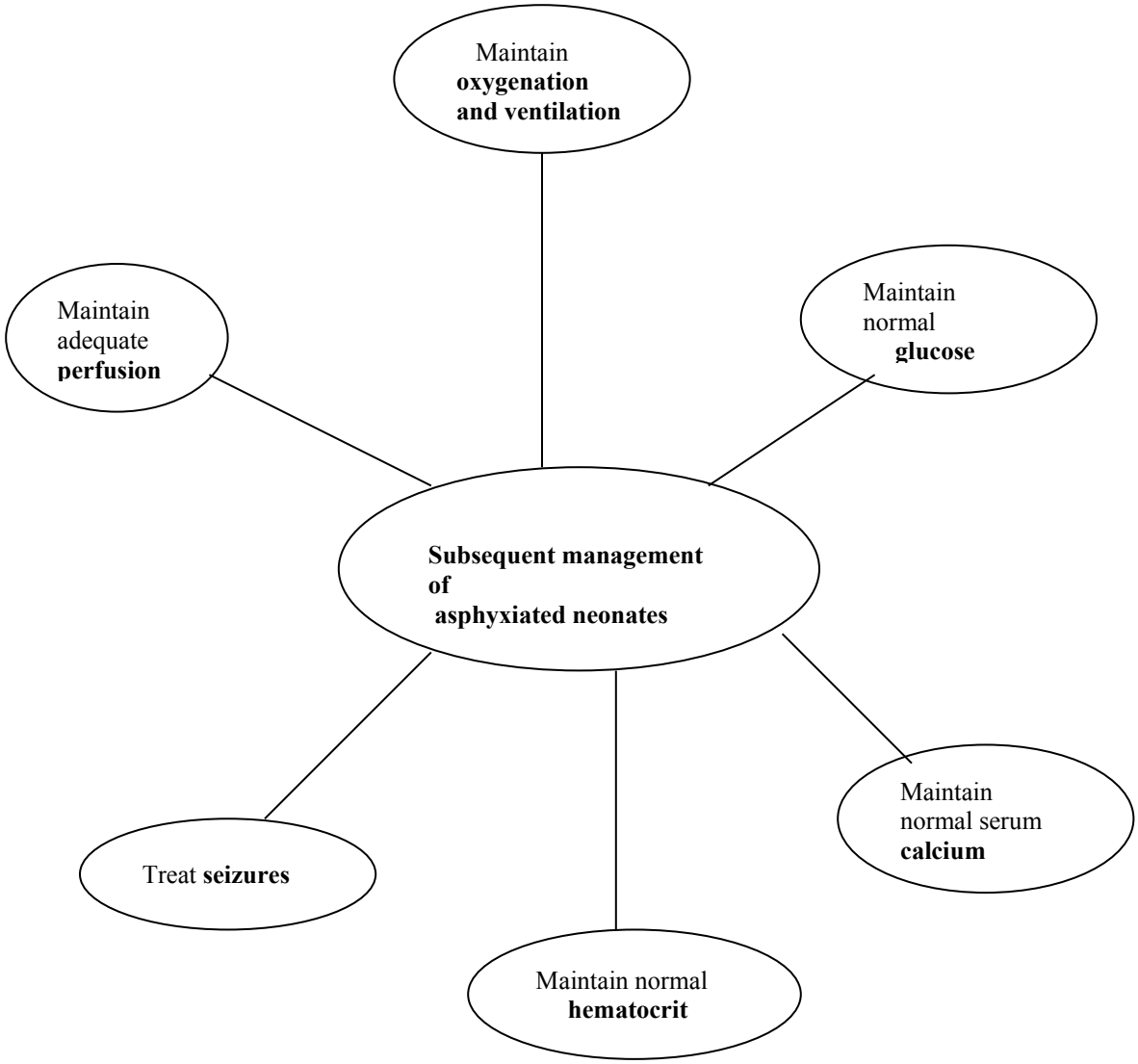

Table 1. Organ system dysfunction in perinatal asphyxia

CNS	Hypoxic ischemic encephalopathy, intracranial hemorrhage seizures, long-term neurological sequelae
Cardiac	Myocardial dysfunction, valvular dysfunction, rhythm abnormalities, congestive cardiac failure
Renal	Hematuria, acute tubular necrosis, renal vein thrombosis
Metabolic	Acidosis, hypoglycemia, hypocalcemia, hyponatremia
Pulmonary	Delayed adaptation, respiratory failure, meconium aspiration Surfactant depletion, primary pulmonary hypertension
GI tract	Necrotizing enterocolitis, hepatic dysfunction
Hematological	Thrombocytopenia, coagulation abnormalities

Table 2: Classification of HIE (Levene)[6]

Feature	**Mild**	**Moderate**	**Severe**
Consciousness	Irritable	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain spontaneous respiration