Post-resuscitation management of asphyxiated **neonates**

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Abstract

Inspite of major advances in monitoring technology and knowledge of fetal and perinatal medicine, Perinatal asphyxia is one of the significant causes of mortality and long term morbidity. 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.

Key words : Asphyxia, HIE,

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). Some experts prefer to use tern neonatal encephalopathy , as it is not always possible to document the hypoxic ischemic insult and there may be potential several other etiologies operating. HIE is of concern in an asphyxiated neonate because it can lead to serious long-term neuro-motor sequelae among survivors.

Definition

A gold standard definition of birth asphyxia does not exist. It is probably better to use the term perinatal asphyxia since asphyxia may occur in utero, at birth or in the postnatal 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.

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As per the AAP (American academy of Pediatrics) and ACOG (American college of Obstetrics and Gynecology), all the following must be present for designation of asphyxia Viz (a) Profound metabolic or mixed academia (pH< 7.00) in cord. (b) Persistence of Apgar scores 0-3 for longer than 5 minutes. (c) Neonatal neurologic sequelae (eg, seizures, coma, Hypotonia). (d) Multiple organ involvement (eg, of the kidney, lungs, liver, heart, intestine) 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 continued 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 leads to muti-organ dysfunction. Virtually any organ can be effected. And care in the nursery should be oriented to determining the presence or the absence of dysfunction of the critical organ 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 1).

Metabolic involvement may include hypocalcemia, hyponatremia (as a result of SIADH or direct renal injury), and alterations in glucose metabolism. There may be haematological alterations (thrombocytopenia and DIC)

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 (phase of energy failure) 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. The duration of this 'delayed phase of neuronal injury ' is not

known precisely, but appears to increase over first 24 to 48 hours and than starts to resolve . Thus 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. Additional factors that may influence the outcome include the nutritional satus of the brain, severe intrauterine restriction, preexisting brain pathology, and the frequent siezuure disorder that anifest in the early postnatal age (within hours of birth)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. All these bsbies should have a cord gas analysis performed .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. Adverse outcomes have been associated with pyrexia in these newborns, hence it is to be avoided[15] 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.

The therapeutic hypothermia as a modality to prevent disability is a new evolving therepy. The combination of the three main trials suggest that mild hypothermia is associated with significant reduction in deaths and severe disability following asphyxia . Therapeutic hypothermia for encephalopathic asphyxiated newborn infants should be only administered in well designed randomized controlled trials as of now.[16, 17, 18] as many of the aspects of hypothermia need to be optimized and refined, and the magnitude of the risk versus the benefit when applied to the population of the infants with HIE has yet to be established.

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. Current recommendations to restrict fluid input are based mainly on data from the treatment of adults and older children, or from animal models of cerebral hypoxia. The rationale is that fluid restriction may limit cerebral oedema, which may be important in the pathogenesis of brain damage after perinatal asphyxia. However, there is

concern that excessive fluid restriction may cause dehydration and hypotension, resulting in decreased cerebral perfusion and further brain damage.[19]

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.

Maintain the blood gases and acid-base status in the physiological ranges including partial pressure of arterial oxygen (PaO_2), 80-100 mm Hg; partial pressure of arterial carbon dioxide ($PaCO_2$), 35-40 mm Hg; and pH, 7.35-7.45.

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. Maintain the mean BP above 35 mm Hg (for term infants). Dopamine or dobutamine can be used to maintain adequate cardiac output. *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 may 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). The renal function studies (serum creatinine, creatinine clearance, and BUN) may be estimated if required. Cardiac and liver enzymes values are an adjunct to assess the degree of hypoxic-ischemic injury to these other organs. These studies also provide some insight into injuries to other organs, such as the bowel.

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.

Amplitude-integrated electroencephalography (aEEG): Several studies have shown that a single-channel aEEG performed within a few hours of birth can help evaluate the severity of brain injury in the infant with HIE. While a normal aEEG may not necessarily mean that the brain is normal, a severe or moderately severe aEEG abnormality may indicate brain injury and poor outcome. The abnormalities include wide fluctuations in the amplitude with the baseline voltages dropping to near zero and the peak amplitudes under 5 mV. Seizure spikes may be seen.[15] Although many centers are using aEEG, note that considerable training is required for conducting and properly interpreting the aEEG tracings.

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.

Magnetic resonance maging: MRI provides prognostic information, The findings of abnormalities of thalami and ganglia in term, White and grey matter abnormalities at term equivalent in preterms are strong predictors of subsequent risk of poor neurodevelopmental outcome[14] It is important to understand that MRI is preferred over CT as it has a greater interobserver agreement and no radiation exposure.

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.

ECHO; In infants needing ionotropic support, an ECHO at times may give an insight into the contractinbility and the asphyxial injury to the heart (MR,)and guide appropriate management strategy.

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,

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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 the Cochrane review database systematic review by Evans et al (2000) that included the 5 RCTs derived no difference in the risk of death , neurodisability[20]. Another study using 40 mg/kg within 1st hour showed a significant reduction in HIE with no difference in complications.[21] 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.. *It may be noted that none of the modalities mentioned in this section are ready for routine use as yet.*

4. Followup

All the neonates with the moderate and severe asphyxia , especially those with stage II and III HIE staging should be followed in the High risk clinic, they should have a complete neurological assessment and intervention if needed during the followup. A formal psychometric assessment at 18months should be performed in all these babies

5. Long term outcome

Among the infants who survive severe HIE, the sequelae include mental retardation, epilepsy, and cerebral palsy of varying degrees. The latter can be in the form of hemiplegia, paraplegia, or quadriplegia. Such infants need careful evaluation and support. They may need to be referred to specialized clinics capable of providing coordinated comprehensive follow-up care.

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The incidence of long-term complications depends on the severity of HIE. Up to 80% of infants who survive severe HIE develop serious complications, 10-20% develop moderately serious disabilities, and up to 10% are normal. Among the infants who survive moderately severe HIE, 30-50% may suffer from serious long-term complications, and 10-20% with minor neurological morbidities. Infants with mild HIE tend to be free from serious CNS complications
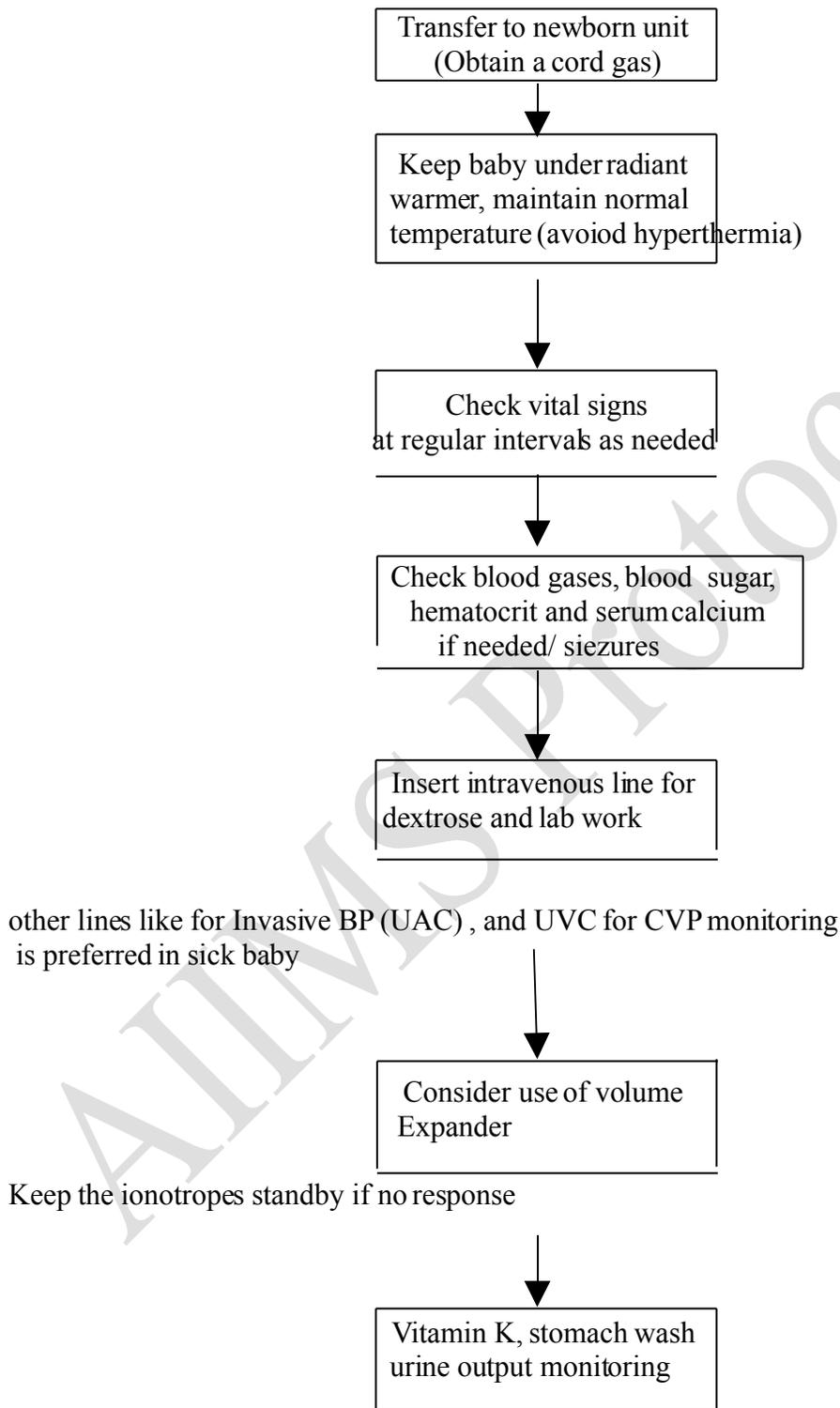
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Fig 1: Summary of *initial management* of asphyxiated neonates

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          ┌─────────────────────────────┐
          │   Transfer to newborn unit   │
          │     (Obtain a cord gas)      │
          └─────────────────────────────┘
                        │
                        ▼
          ┌─────────────────────────────┐
          │  Keep baby under radiant     │
          │  warmer, maintain normal     │
          │ temperature (avoided          │
          │ hyperthermia)                │
          └─────────────────────────────┘
                        │
                        ▼
          ┌─────────────────────────────┐
          │      Check vital signs       │
          │ at regular intervals as needed│
          └─────────────────────────────┘
                        │
                        ▼
          ┌─────────────────────────────┐
          │ Check blood gases, blood sugar,│
          │  hematocrit and serum calcium │
          │      if needed/ siezures      │
          └─────────────────────────────┘
                        │
                        ▼
          ┌─────────────────────────────┐
          │  Insert intravenous line for  │
          │   dextrose and lab work       │
          └─────────────────────────────┘
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other lines like for Invasive BP (UAC) , and UVC for CVP monitoring
is preferred in sick baby

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          ┌─────────────────────────────┐
          │   Consider use of volume     │
          │   Expander                   │
          └─────────────────────────────┘
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Keep the ionotropes standby if no response

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          ┌─────────────────────────────┐
          │  Vitamin K, stomach wash     │
          │  urine output monitoring     │
          └─────────────────────────────┘
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Calcium (40mg/kg) is started in babies with severe birth asphyxia prophylactically

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

Maintain **oxygenation and ventilation**

Maintain adequate **perfusion**

Maintain normal **glucose**

Subsequent management of asphyxiated neonates

Treat **seizures**

Maintain normal serum **calcium**

Maintain normal **hematocrit**
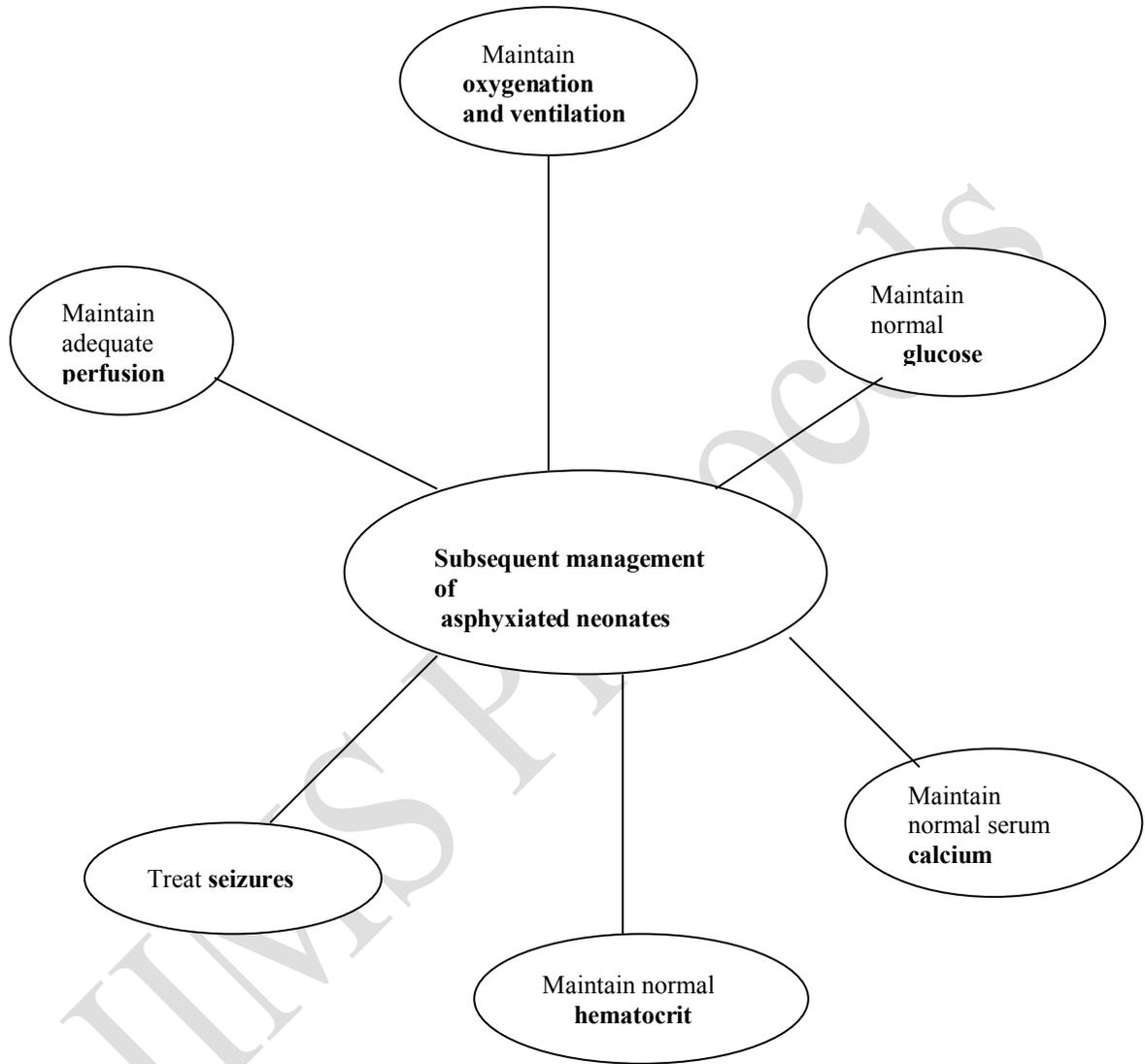
Table 1. Organ system dysfunction in perinatal asphyxia

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