Editorial

DIAGNOSIS AND MANAGEMENT OF PERINATAL ASPHYXIA: CURRENT CONCEPTS

Perinatal asphyxia is one of the leading causes of perinatal deaths and a recognized cause of neuromotor disability later in life among the survivors. Birth asphyxia and hypothermia are known to predispose the baby to develop a large number of neonatal disorders affecting almost every system of the baby thus increasing neonatal morbidity(l). Effective and optimal management of every baby at birth is one of the most effective strategy for reducing neonatal morbidity and enhancing newborn survival.

What is the Definition of Perinatal Asphyxia or Birth Asphyxia?

Asphyxia refers to a combination of hypoxia, hypercarbia and metabolic acidosis as a consequence of occlusion of umbilical vessles or interference with placental perfusion in fetal life and/or due to lack of effective breathing after birth. There is no unanimity or consensus regarding the definition of birth asphyxia and various workers have used different definitions(2) *(Table I).*

The National Neonatology Forum of India has proposed that "gasping and ineffective breathing or lack of breathing at 1-minute" should be designated as birth asphyxia(3). By virtue of its simplicity it can be used even in the community setting. It corresponds to 1-minute Apgar score of less than 4 and is acceptable for calculating the incidence of birth asphyxia and should be used by all centres in the country. However, most babies with 1-minute Apgar score of less than 4 do not need specialized care in the nursery and generally do not develop any neuromotor sequelae on follow up if they were stable and had established effective breathing by 5 minutes. The incidence of birth asphyxia varies between 0.5-8.5% in different studies due to differences in the study population and lack of a uniform standard definition(4,5).

Management

Every birth must be considered as a medical emergency and optimal infrastructure and basic equipment for resuscitation should be available in working order before the birth of the baby. The personnel attending the delivery should be skilled in the art of neonatal resuscitation. After resuscitation, the asphyxiated baby should be provided with specialized supportive management and followed up for assessment of

TABLE I— *Various Definitions of Perinatal Hypoxia and Birth Asphyxia*

1. Apgar score of <4 at 1-min or 5-min or 10-min or later
2. Gasping or no breathing at 1-min or 5-min or 10-min or later
3. Time taken to establish spontaneous breathing after birth
4. Umbilical cord arterial pH <7.0
5. Evidences of hypoxic-ischemic encephalopathy
6. Evidences of multiorgan dysfunction

neuromotor development. If 5-minute Apgar score is less than 4, *i.e.,* the baby failed to establish effective breathing by 5 minutes of age, the baby should be closely monitored clinically, biochemically and by laboratory investigations to identify evidences of hypoxic damage to various organs of the baby. Vital signs should be monitored preferably with the help of multichannel vital sign monitor. The evidences of hypoxic-ischemic damage to the central nervous system should be assessed and graded with the help of Sarnat staging system(6). Renal perfusion should be monitored by recording urine output which should be maintained above 2 ml/kg/h. Acid base parameters and blood gases should be monitored as soon as the infant is transferred to the nursery. Blood glucose should be frequently checked to identify hypoglycemia and hyperglycemia(5,7). Hyponatremia due to inappropriate secretion of antidiuretic hormone and hyperkalemia due to tissue catabolism and acute renal shut down are common and should be monitored(8). Tissue injury as a consequence of perinatal hypoxia leads to release of phosphate in the blood stream with development of hypocalcemia because of inverse relationship between calcium and phosphate. Prolongation of QoTC >0.2 seconds on EKG is a useful non-invasive rapid means of diagnosing hypocalcemia in a newborn baby. Severe birth asphyxia is also associated with elevation of lactate and pyruvate, brain-specific creatine kinase (CK-BB), adenine derivatives (hypoxanthine) and non-esterified free fatty acids but these parameters are more often used as research tools. Skiagram of chest should be taken in all cases to exclude pneumothorax, diaphragmatic hernia and congenital pneumonia. Availability of cold light transilluminator is useful for prompt diagnosis of pneumothorax in the labor room.

Supportive Management

The infant should be nursed in a thermoneutral environment by keeping him in a servo-controlled infant care system in order to reduce consumption of energy and oxygen for metabolic thermogenesis. Due to the danger of cerebral edema and retention of fluids as a consequence of SIADH, the maintenance fluid requirements should be restricted to two-third of the normal(7). It is preferable to administer 10% dextrose solution and no electrolytes should be administered during first 48 hours of life. Acidosis, hypoglycemia, hypocalcemia (QoTC >0.2 second) and hyperkalemia should be identified and appropriately managed. Blood glucose should be maintained between 49-100 mg/dl because both hypoglycemia and hyperglycemia are known to cause damage to the neuronal tissue(9). Among all sources of energy, glucose alone is capable of sustaining energy metabolism in the brain under conditions of total cerebral ischemia because of its capacity for consumption via anerobic glycolysis with the production of lactic acid and ATP. However, during anerobic conditions one molecule of glucose yields only 2 molecules of ATP as opposed to 38 molecules of ATP during aerobic metabolism. Hypotension and poor tissue perfusion should be identified and promptly managed by administration of normal saline, fresh frozen plasma or albumin and by use of small doses of dopamine or dobutamine when myocardial dysfunction is strongly suspected. Bolus administration of intravenous drugs or fluids should be avoided as a safeguard against rupture of vulnerable capillaries in the germinal matrix of brain and in the lungs. Routine administration of antibiotics to all asphyxiated babies is unnecessary and they are indicated either when perinatal risk score for infection

is high or sepsis screen is suggestive of bacterial infection. Vitamin K in a dose of 0.5-1.0 mg should be administered intramuscularly to all asphyxiated babies to correct any coagulation abnormalities.

Brain-oriented Resuscitation

Infants with absence of spontaneous breathing efforts by 10 minutes or those with clinical evidences of hypoxic-ischemic encephalopathy demand more energetic measures to reduce cerebral edema, improve cerebral perfusion and prevent further on-going neuronal damage due to hypoxia, ischemia and metabolic disturbances. The baby should be nursed with head raised by 30° to prevent further elevation of intracranial pressure. The infant should be intubated and attached to a mechanical ventilator and provided with hyperventilation to maintain paO_2 above 100 mm Hg. Hypocarbia ($paCo_2$ between 25-35 mm Hg) should be maintained to prevent vasodilatation and is extremely useful to reduce intracranial pressure. Mannitol 20% solution in a dose of 0.5-1.0 g/kg should be administered over a period of 15 minutes and repeated every six hours during the first 24 hours of life(10,ll). Furosemide in a dose of 1.0 mg/kg every 12 hours intravenously for 4 doses is recommended especially when there is oliguria to ensure diuresis and reduce intracranial pressure. The use of corticosteroids is not recommended for the treatment of hypoxic-ischemic encephalopathy. In an animal study, it has been shown that high dose steroid therapy was associated with increased mortality and it interfered with brain development in perinatal animals(12).

There is controversial evidence that prophylactic administration of phenobarbitone at birth in severely asphyxiated babies may be associated with improved survival and reduced risk of neuromotor disability(13). It has been shown in rats that phenobarbitone improves CNS metabolism, improves integrity of neurons and raises threshold for seizures. It is recommended to administer a loading dose of phenobarbitone 20 mg/kg followed by 5 mg/kg/d as maintenance dose intravenously. In a double blind controlled trial, we have demonstrated that prophylactic administration of phenobarbitone is associated with improved neuromotor outcome especially in severely asphyxiated babies(5). However, prophylactic administration of phenobarbitone is still controversial and it should be tried only in centres which are equipped to provide assisted ventilation. Therapeutic utility of phenobarbitone in infants who develop seizures following birth asphyxia is unquestionable and it is anticonvulsant of choice for management of HIE-related seizures once metabolic conditions are excluded or appropriately managed.

Newer Treatment Modalities

The understanding of current pathogenetic mechanisms of hypoxic-ischemic injury to the brain has resulted in identification of newer modalities of treatment(14,15). They may help in preventing on-going neuronal cell injury though most of them are at an experimental stage as yet.

Oxygen Free Radical Inhibitors and Scavengers

Oxygen free radicals are implicated as pathogenetic mediators in many neonatal disorders including HIE. Free radicals are known to initiate and perpetuate a cascade of chain reactions(16). During hypoxic-ischemic insult, free radicals are produced by the process of degradation of ATP. On reperfusion of the tissues, xanthine oxidase metabolises molecular oxygen to produce oxygen free redicals. Drugs that inhibit the formation of oxygen free radicals or that

rapidly destroy the free radicals have been tried to prevent brain damage due to hypoxic-ischemic insult. Administration of specific enzymes including superoxide dismutase (SOD), endoperoxidase and catalase to degrade highly reactive radicals to non-reactive components and use of scavengers of oxygen free radicals like vitamin E, vitamin C and mannitol have been shown to improve neurological outcome and decrease biochemical markers of brain injury in animals. Drugs that are known to inhibit the specific reaction in the production of prostaglandins and xanthine may indirectly lower the formation of oxygen free radicals. Indomethacin, a cycloxygenase and phospholipase A2 inhibitor and allopurinol, a xanthine oxidase inhibitor, have been shown to be of benefit in ischemic neuronal or myocardial damage in animals. Palmer *et al.* have shown that treatment with allopurinol before asphyxial insult reduces both brain swelling and structural damage to the perinatal brain(17).

Calcium Channel Blockers

Sudden influx of calcium ions inside the neurons is believed to cause neuronal damage during HIE. Calcium activates several lipases, proteases and endonucleases. High intracellular concentration of calcium ions results in uncoupling of oxidative phosphorylation within mitochondria leading to depleted stores of adenosine triphosphate in cytosol. Calcium also contributes to the formation of oxygen-free radicals by production of xanthine oxidase, nitric oxide and prostaglandins. Among the available calcium channel blockers, flunarizine and nimodipine appear most efficacious in adult animals(18). Using a rat model, two studies have shown an amelioration of neuropathologic alterations in animals pretreated with flunarizine(19,20).

Excitatory Amino Acid Antagonists

Of the various neurotransmitters known to exist in brain, the amino acid glutamate is now considered as one of the major endogenous excitatory neurotransmitter. Asphyxia causes excessive release of glutamate from presynaptic vesicles and inhibits uptake of glutamate from the synaptic cleft(21). Excessive exposure of neurons to glutamate leads to neuronal injury. Animal experiments have shown that direct injection of glutamate into the specific regions of brain *in-vivo* produces neuronal injury identical to that seen after hypoxic brain damage. Baclofen, an inhibitor of glutamate release, has not been evaluated for its therapeutic utility. Other agents like phencyclidine, dextromethorphan, ketamine, MK-801 which affect N-methyl-D-aspartate (NMDA) have been tried in experimental animals with variable results(22). The protective role of MK-801, administered before producing hypoxic injury, appears greater in immature-rats as compared to their adult counterparts(23). Unfortunately, MK-801 and NMDA receptor antagonists are highly toxic. Magnesium appears to be a naturally occurring antagonist of NMDA which has a receptor site deep within calcium channel. It has been suggested that increasing the extracellular neuronal concentration of magnesium may protect the brain against hypoxic-ischemic insult by an action similar to NMDA receptor antagonists. The role of magnesium sulphate as a neuroprotective agent for prevention of brain damage due to hypoxia-ischemia, deserves active consideration and evaluation.

Prevention of Excess Nitric Oxide Formation

Nitric oxide is a free radical gas that can be rapidly produced by a nitric oxide

ynthase enzyme in cerebral endothelial cells and neurons in response to an increase in intracellular calcium. Trifiletti(24) showed that administration of nitro arginine 15 hours prior to cerebral hypoxia-ischemia in immature rats caused prolonged inhibition of nitric oxide synthesis and reduction in the extent of brain injury.

Future Areas of Research

The identification of newer pathogenetic mechanisms for causation of neuronal injury due to HIE has opened possibilities for trial and evaluation of newer therapeutic modalities. However, newer modes of therapy for HIE are still in an experimental stage and they are not recommended for routine use in clinical practice. In view of the implication of oxygen free radicals in the causation of brain injury following reperfusion, there is a need to evaluate the resuscitation of asphyxiated newborn babies with room air versus 100 per cent oxygen in a double-blind randomized controlled study(25). The therapeutic utility of following treatment modalities needs to be evaluated in double-blind controlled clinical trials *e.g.,* glucose, phenobarbitone, mannitol, allopurinol, calcium channel blocking agents, magnesium sulphate *etc.* Prophylactic utility of brain "tonics" such as pyritinol dihydrochloride monohydrate, piracetam, *mentat, etc.* to reduce neuromotor disability following severe birth asphyxia also needs to be evaluated by double-blind controlled clinical studies.

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