"STUDY ON SHORT-TERM OUTCOME OF BIRTH ASPHYXIA TREATED WITH MAGNESIUM"

Submitted by

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Dissertation submitted to the

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In Partial Fulfillment Of The Requirements For The Degree Of

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UNDER THE GUIDANCE OF

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LIST OF ABBREVATIONS USED

LSCS	Lower Segment Caesarian Section
IV	Intra Venous
CNS	Central Nervous System
NMDA	N-Methyl-D-Aspartate
CSF	Cerebrospinal fluid
HIE	Hypoxic ischemic encephalopathy
SD	Standard Deviation
NO	Nitric Oxide
GMH	Germinal Matrix Hemorrhage
IVH	Intra Ventricular Hemorrhage
PAH	Pulmonary Artery Hemorrhage
FI	Feed intolerance
HYB	Hyperbilirubinemia
NRP	Neonatal resuscitation programme
EEG	Electroencephalography
CT	Computed Tomography
MRI	Magnetic resonance imaging
CSF	Cerebro-Spinal fluid
USG	Ultra-Sonography
AAS	Absorption Spectrometry
CVP	Central venous pressure
MBP	Mean blood pressure
CPP	Cerebral Perfusion Pressure

ICT	Intra Cranial Tension
Hrs	Hours
mmHg	Millimeters of Mercury
mEqL	Milliequalence per liter
mcg	Microgram
S.Mg	Serum Magnesium
Mg^{2+}	Magnesium
K^{+}	Potassium
Na^{+}	Sodium
$Ca2^{+}$	Calcium

ABSTRACT

INTRODUCTION: Until recently, management strategies of birth asphyxia were supportive and not targeted toward the processes of ongoing injury. In view of conflicting reports about the role of magnesium in birth asphyxia and also due to the paucity of Indian studies in this part of Karnataka, the present study was undertaken.

OBJECTIVE: To study the outcome and complications of term asphyxiated neonates in the first 10 days of life who are supplemented with Magnesium.

METHODOLOGY: Randomized case control study on 85 term neonates with birth asphyxia (45 cases and 40 controls). All the term neonates with Apgar score of 3 or less at 1minute and 6 or less at 5 minutes were included in the study. Cases had received Magnesium Sulfate intravenous infusion at a dose of 250 mg/kg in first hour of life and 2 additional doses of 125 mg/kg at intervals of 24 hours. Serum Magnesium was estimated at birth and then on 12, 24, 48 and 72 hours of life in both groups.

RESULTS: Mean number of convulsions was 4.6 in cases and 7.2 in control group. Time interval between the first and last convulsion was less in cases as compared to control group. Duration of Oxygen supplementation and NICU stay were significantly shorter in cases. Direct breast feeding was able to initiate early in cases as compared to controls group. Significant differences in Magnesium level were seen in cases after supplementation. Clinical or Serum Magnesium toxicity were not detected in any of the cases. There was no difference in incidence of complications among the two groups

CONCLUSION: Decrease in the number of convulsion and duration of convulsion shows the neuroprotective effect of Magnesium in treatment of birth asphyxia. In the present study magnesium supplementation regimen was not associated with toxicity.

Key Words: Birth Asphyxia, Magnesium supplementation, Neuroprotection

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INTRODUCTION

In spite of major advances in monitoring technology and knowledge of fetal and perinatal medicine; birth asphyxia is one of the significant causes of mortality and long term morbidity. Data from National Neonatal Perinatal database suggests that birth asphyxia contributes to almost 20% of neonatal deaths in India. 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. “Failure to initiate or sustain respiration after birth” is defined as criteria for the diagnosis of asphyxia by WHO.

Strict monitoring and prompt correction is needed for common problems including temperature maintenance, blood sugar, blood pressure and oxygenation . Birth asphyxia may occur in utero, during labour and delivery, or in the immediate postnatal period. The clinical and neurological sequelae following perinatal asphyxia is referred to as Hypoxic-Ischemic Encephalopathy (HIE). Most widely used classification of HIE is that of Sarnat and Sarnat which divides affected infants into Stage I, Stage II and Stage III

As of now, the management of an asphyxiated newborn is limited to early identification of the infant at highest risk and supportive care to facilitate adequate perfusion and nutrients to the brain. The neuroprotective strategies aimed at ameliorating secondary brain injuries are hypothermia, oxygen free radical scavengers and excitatory amino acid antagonists.

In birth asphyxia, glutamate, the main excitatory amino acid neurotransmitter, is released in increased concentrations in the extracellular compartment of brain. N-Methyl-D-Aspartate (NMDA) receptor is particularly important in the development of post-asphyxial neuronal injury. High concentrations of glutamate cause the NMDA channels to open, allowing excessive amounts of calcium into the neurons, inducing irreversible cell injury. Magnesium ions gate the NMDA channel in a voltage dependent manner by producing hyperpolarization, and increasing the extracellular Mg^{2+} concentration may protect the brain from NMDA receptor mediated damage.

Magnesium is a naturally occurring NMDA receptor antagonist protecting the developing brain from the damage usually which is caused by glutamate. Thus magnesium sulphate is proposed for clinical use to combat glutamate excitotoxicity and brain damage. So far, to the best of our knowledge, only two published study in India regarding the role of magnesium therapy in birth asphyxia.\ Both were randomized controlled trials done in 2006 and 2009 which concluded neurological abnormalities were less frequent in those neonates treated with magnesium.

But there is a paucity of data from this part of India regarding the role of magnesium therapy in perinatal asphyxia. In view of conflicting reports about the role of magnesium in perinatal asphyxia and also in view of paucity of Indian studies in this subject, the present study was undertaken.

OBJECTIVES

1. **To study neonatal outcome and advantages of early supplementation of magnesium in birth asphyxia.**

2. **To study the complications of term asphyxiated neonates in the first 10 days of life.**

REVIEW OF LITERATURE

The literature in this subject began with the paper by William John Little "On the nature and treatment of deformities of the human frame." Published in 1853 for the first time he described four cases of spasmodic affection, which he thought to have occurred due to difficulty and slowness of parturition in which the babies were asphyxiated and demanded resuscitation for several hours following birth.[11]

Later in 1862 Little wrote further on "The influence of abnormal parturition, difficult labours, premature births and asphyxia neonatorum on mental and physical condition of child especially in relation to deformities".[12]

Sheriberin 1938 suggested that some of cerebral lesions considered to be congenital and may be sequel of birth injury and asphyxia.[12]

Potter in 1940 differentiated the concept of "Birth trauma" from "asphyxia" since these entities include any condition which affect fetus adversely during delivery. Potter then distinguished these two conditions. Fetal damage caused by primary inadequacy of oxygen in the circulation and that caused by mechanical injury. Under birth trauma he included hemorrhages resulting form contusions, laceration or fracture and under asphyxia only primary oxygen insufficiency. [12]

In 1941 Curville thought that a variety of lesions are responsible for idiopathic infantile diplegia and epilepsies of indefinite etiology are caused by at least to considerable extent by neonatal asphyxia.

Symposium on birth asphyxia in 1944 not agreeable to correlate asphyxia at birth with injury to CNS based on clinical evidence[12] but the term anoxia and asphyxia have been used synonymously.

Evans in 1948 supported the cause of congenital diplegia in difficult labour. Asher and Schonell in 1950 concluded that athetosis was usually the result of birth injury or asphyxia or a neonatal jaundice.[12] Neonatal asphyxia is one of the most common cause of fetal and neonatal mortality and morbidity.

Anderson in 1952 studied 1043 deaths and revealed the following percentage of deaths due to anoxia in term and preterm infants.

PATHOPHYSIOLOGY

Perinatal asphyxia is an insult to fetus or newborn due to lack of oxygen (Hypoxia) and/ or lack of perfusion (Ischemia) to various organs of sufficient magnitude and duration to produce more than fleeting functional and/or biochemical changes.

In term infants, 90% of asphyxia insults occur in the antepartum or intrapartum periods as a result of placental insufficiency, resulting in an inability to provide oxygen and to remove carbon dioxide and hydrogen ions form the fetus. The remainder is postpartum, usually secondary to pulmonary, cardiovascular or neurological abnormalities.

A recent review suggests that asphyxia is probably primarily antepartum in origin in 50% of cases, intrapartum in 40% and postpartum in the remaining 10% of cases.[13] However, given the higher incidence of serious complications in labor and reduced availability of skilled care during delivery, it is likely that intrapartum causes account for a larger proportion of cases in developing countries.

During normal labour, uterine contractions and some degree of cord compression result in reduced blood flow to the placenta, and hence decreased oxygen delivery to the fetus. Because there is a concomitant increase in oxygen consumption by both mother and fetus, fetal oxygen saturation falls. Maternal dehydration and maternal alkalosis from hyperventilation may further reduce placental blood flow; maternal hypoventilation may also contribute to decreased maternal and fetal oxygen saturation. These normal events cause most babies to be born with little oxygen reserve. Newborns, however, including their central nervous systems (CNS), are fairly resistant to asphyxic damage. Late decelerations are uncommon until the partial pressure of oxygen (PO2) is less than 20 mmhg. Furthermore, partial asphyxia within hour is unlikely to result in an encephalopathy, defined simply as an altered level of consciousness without etiological implications.

In addition to the normal factors mentioned, any process that:

1. Impairs maternal oxygenation.

2. Decreases blood flow form the mother to the placenta or from the placenta to the fetus.

3. Impairs gas exchange across the placenta or at the fetal tissue or

4. Increases fetal oxygen requirement, will exacerbate perinatal asphyxia.

In presence of hypoxic-ischemic challenge to the fetus, reflexes are initiated, causing shunting of blood to the brain, heart and adrenals and AWAY from the lungs, gut, liver, kidneys, spleen, bone, skeletal muscle and skin (Diving Reflex).

In mild asphyxia there is decreased heart rate, slight increase in blood pressure to maintain cerebral perfusion, increased central venous pressure and little change in

cardiac output. As the asphyxia progresses with severe hypoxia and acidosis, there is a decreased heart rate, decreased cardiac output and initially increased and then falling blood pressure as oxidative phosphorylation fails and energy reserves become depleted. During asphyxia, anaerobic metabolism produces lactic acid, which because of poor perfusion, remains in local tissues. Systemic acidosis may actually be mild until perfusion is restored and these local acid stores are mobilized.[8]

Biochemical changes in perinatal asphyxia [14]

Prominent among the biochemical features of hypoxic ischaemic injury is the loss of cellular ATP, resulting in increased intracellular Na^+, $Ca2^+$, and decreased intracellular K^+. These ionic imbalances, together with a breakdown in cellular defense systems following hypoxic ischemic injury, can contribute to oxidative stress with a net increase in reactive oxygen species. Subsequent damage to lipids, proteins, DNA and inactivation of key cellular enzymes leads ultimately to cell death.

Clinical aspects of perinatal asphyxia

The neonates fulfilling at least on of the intrapartum criteria of fetal distress and one of the neonatal features of asphyxia are defined as having asphyxia.

The intrapartum criteria of fetal distress include:

a. Fetal Heart Rate Abnormalities: Fetal bradycardia (<100 beats/min) or fetal tachycardia (>160 beats/min) or abnormal cardiotocographic findings.

b. Presence of meconium stained liquor.

The neonatal criteria include :

a. Need for assisted ventilation for >1 minute for establishment of adequate spontaneous respiratory efforts.

b. Apgar score of <7 at 1 minute of age.

c. Alteration in both tone (Hypo or Hypertonia) and sensorium (obtundation or irritability) during the first day of life not attributable to other causes such as prematurity, sepsis, metabolic disturbances, intracranial hemorrhage etc.[15]

THE APGAR SCORE :

In 1952, Dr Virginia Apgar devised a scoring system that was a rapid method of assessing the clinical status of the newborn infant at 1 minute of age and the need for prompt intervention to establish breathing.[16] This scoring system provided a standardized assessment for infants after delivery. The Apgar score comprises 5 components: heart rate, respiratory effort, muscle tone, reflex irritability, and color, each of which is given a score of 0, 1, or 2. The score is now reported at 1 and 5 minutes after birth.

The neonatal resuscitation program (NRP) guidelines[17] state that Apgar scores should not be used to dictate appropriate resuscitative actions, nor should interventions for depressed infants be delayed until the 1-minute assessment." The current NRP guidelines[17] state "if there is no heart rate after 10 minutes of complete and adequate resuscitation efforts, and there is no evidence of other causes of newborn compromise, discontinuation of resuscitation efforts may be appropriate. Current data indicate that, after 10 minutes of asystole, newborns are very unlikely to survive, or the rare survivor is likely to survive with severe disability."

Apgar Score[19]

Sign	0	1	2	Physiological significance
Heart rate	Absent	Below 100	Above 100	Maybe more easy to palpate the cord pulse than to auscultate
Respiratory effort	Absent	Slow, irregular	Good, crying	
Muscle Tone	Flaccid	Some flexion of extremities	Active motion	May be affected by prematurity, drugs, illness, and other neuromuscular problems.
Reflex irritability	No response	Grimace	Vigorous cry	May be affected by prematurity, drugs, and exact mode of elicitation.
Color	Pale	Cyanotic	Completely pink	Limited, acrocyanosis is common in newborns immediately after birth and score of 2 is rare

Apgar score and resuscitation

The 5-minute Apgar score, and particularly a change in the score between 1 and 5 minutes, is a useful index of the response to resuscitation. If the Apgar score is less than 7 at 5 minutes, the NRP guidelines state that the assessment should be repeated every 5 minutes up to 20 minutes.[17]

Prediction of outcome

A low 1-minute Apgar score alone does not correlate with the infant's future outcome. Moster D et al[21] study that low Apgar scores at 5 minutes are associated with death or cerebral palsy, and this association increased if both 1- and 5 minute scores were low.

A 5-minute Apgar score of 7 to 10 is considered normal. Scores of 4, 5, and 6 are intermediate and are not markers of increased risk of neurologic dysfunction. Such scores may be the result of physiologic immaturity, maternal medications, the presence of congenital malformations, and other factors. Factors including non-reassuring fetal heart rate monitoring patterns and abnormalities in umbilical arterial blood gases, clinical cerebral function, neuroimaging studies, neonatal electroencephalography, placental pathology, hematologic studies, and multisystem organ dysfunction need to be considered when defining an intrapartum hypoxic – ischemic event as a cause of cerebral palsy.[22]

Cord blood gas

The normal cord blood gas values of the fetus are important ot know to interpret gases after delivery.[23]

Normal Cord blood gases

	pH	PaO_2	$PaCO_2$	HCO_3
	(mmhg)	(mmgh)	mEq/L)	
Umbilical artery	7.27+0.08	25+19	45+10	22+3.7
Umbilical Vein	7.34+0.07	36+10	40+6	23+2.2

During the course of normal labor, the PaO_2 drops, the $PaCO_2$ rises, and the base deficit rises. In most centers, a pH of more than 7.2 is considered normal and a pH of 7 to 7.2 considered mild or moderate academia. Severe academia is when the pH is below 7 and there is a base deficit of more than 12 nM.

Some studies suggest that neurologic injury is more likely to occur in an infant who is depressed but has a normal pH.[24 25] Hermansen[26] suggested there is an acidosis paradox or a beneficial effect of a mild to moderate acidosis. One of the possible beneficial effects is that hypercarbia may result in cerebral vasodilatation and increased cerebral blood flow. Second, acidosis has been shown to decrease cerebral metabolism and lower the oxidative needs of the brain. Finally, acidosis promotes the unloading of oxygen from the fetal hemoglobin by shifting the oxygen dissociation curve. These three mechanisms theoretically lead to an adequate amount of oxygen delivery to the brain tissue, which potentially limits damage. These protective effects would be lost, however, with severe acidosis, which can lead to decreased cardiac output and cerebral ischemia.[27] One study suggested that the risks of neonatal seizures and long-term motor or cognitive functions worsen as the pH decreases further below 7.[28]

CLINICAL PRESENTATION AND EXAMINATION

Once an infant is resuscitated, the Apgar scores assigned, and the cord blood gas results returned, the pediatrician must observe the infant and monitor for end organ dysfunction. The cardio respiratory system may require support for respiratory distress syndrome or pulmonary hypertension. The goal in management of the respiratory system is moderation in oxygen and carbon dioxide levels. Hypoxia and hyperoxia can lead to further neuronal injury. Hypercarbia can lead to cerebral vasodilation and hemorrhage, whereas hypocarbia can lead to decreased cerebral blood flow.

The cardiovascular system may need support because of myocardial ischemia, poor contractility from the acidosis, tricuspid insufficiency often from pulmonary hypertension, and hypotension. Moderation is best; it helps to avoid hypotension and hypertension because the cerebral vasculature is pressure passive. Infants with any cardio respiratory conditions need neonatal intensive care and require transport for management.

Gastrointestinal damage might include injury to the bowel wall, which can be mucosal or full thickness and even involve perforation. The extent of the damage influences the nutritional management, in particular when to begin feedings once recovery occurs. It might be prudent to allow 3 days of healing for mucosal injury and 7 days for more extensive damage before attempting enteral feeding. The liver can be injured, as measured by elevated transaminases. The liver and bowel typically heal over time and cannot be treated other than through cardio respiratory support and time.

The hematological system also can be affected. In the first hours to days of life, this is manifest through disseminated intravascular coagulation. The infant might need to be supported with blood products over the first few days of life to prevent pulmonary or intracranial hemorrhage. If the bone marrow itself had an ischemic injury, the first sign of marrow suppression would be thrombocytopenia at approximately 5 to 7 days of age, because platelets have the shortest half-life of the marrow products. The marrow recovers over time.

Metabolic abnormalities that are often seen include hypoglycemia, hypocalcemia, myoglobinuria, and inappropriate secretion of antidiuretic hormone, which leads to hyponatremia. These abnormalities must be treated to prevent worsening seizures.[29]

The kidney often has been thought to be the window to the brain in this disease. One study revealed that if an infant had good urine output, the chances of mortality and neurologic injury were 5% and 10%, respectively, whereas oliguria beyond 24 hours resulted in rates of mortality and neurologic injury of 33% and 67%, respectively.[30] Acute tubular necrosis has not proved to be as a good predictor of mortality and neurologic injury as initially believed.[31] Management of acute tubular necrosis is through fluid restriction once volume status has been maximized.

The central nervous system is the central focus when discussing asphyxia. Injury can occur through focal intracranial hemorrhage or infarction or the more global injury of hypoxic-ischemic encephalopathy. These injuries typically are evaluated by neurological examination, electroencephalography (EEG), and imaging (either CT scan or MRI).[29]

Three clinical stages of encephalopathy, known as the Sarnat stages, have been characterized and can predict outcome.[32]

Stage I lasts less than 24 hours and is characterized by hyperalertness, uninhibited Moro and stretch reflexes, sympathetic effects, and a normal electroencephalogram. Stage 2 is marked by obtundation, hypotonia, strong distal flexion, and multifocal seizures. Infants in stage 3 are stuporous and flaccid, and brain stem and autonomic functions are suppressed.

Sarnat and Sarnat stages of HIE

Stage	**Stage I (Mild)**	**Stage II (Moderate)**	**Stage III (Severe)**
Level of consciousness	Hyper alert; imitable	Lethargic or obtuned	Stuporous or comatose
Neuromuscular control	Uninhibited, overactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overacitve, disinhibited	Decreased or absent
<u>Complex reflexes</u>	Normal	Supressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high	Absent
Tonic neck	Slight	Threshold Strong	Absent

Autonomic functions Pupils Respiration Heart rate Bronchial and Salivary secretions	Generalized sympathetic Mydriasis Spontaneous Tachycrdia Sparse	Generalized parasympathetic Miosis Spontaneous, occasional apnea Bradycardia Profuse	Both systems depressed Variable, often unequal, poor light reflex Periodic, apnea Variable Variable
Seizures	None	Common, focal or multifocal (6-24 hours of age)	Uncommon (excluding decerebration)
EEG findings	Normal (awake)	Early : generalized low voltage, slowing Later: periodic pattern (awake); seizures focal or multifocal;	Early: periodic pattern with isopotential phases Later : totally isopotential
Duration of symptoms	Less than 24 hours	2 to 14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5 to 7 days	About 50% die; remainder with severe sequelae

The severity of the neurologic syndrome, the presence of seizures, and the duration of the abnormalities provide the best prediction of prognosis. Sarnat and Sarnat[32] found that infants who have signs of stage 2 for less than 5 days have normal outcome. Persistence of stage 2 for more than 7 days or stage 3 at any time is associated with later neurologic impairment or death.[33] Other researchers have confirmed that although the overall incidence of death or sequelae is 27%, if the neurologic syndrome is mild there are no later deficits. When the neurologic syndrome is mild there are no later deficits. When the neurologic syndrome was severe, 80% of infants died and the remaining 20% had significant sequelae.[34, 35] Seizures increase the risk of neurologic sequelae two to fivefold. Data support the theory that if a newborn's neurologic examination returns to normal by 1 to 2 weeks, the infant likely will be normal at follow up. [32,33,35,36]

Thompson score [38] determines encephalopathy as mild, moderate or severe according to modified Sarnath encephalopathy grade[39]. Encephalopathy was defined as the presence of one or more abnormal signs in at least three of the following six categories; level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck or Moro), and autonomic nervous system (pupils, heart rate, or respiration). The grades are defined as follows:

Classification of HIE (Levene)[37]

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

Mild : Hyperalert, normal tone and activity, exaggerated moro, normal autonomic function;

Moderate : Lethargic, decreased activity, distal flexion, hypotonia, weak primitive reflexes, constricted pupils, bradycardia or periodic breathing;

Severe: Stupor/coma, decerebrate posture, absent spontaneous activity, flaccid, absent primitive reflexex, non-reactive pupils or apnoea.

HYPOXIC ISCHEMIC ENCEPHALOPATHY

Hypoxic-ischemic cerebral injury that occurs during the perinatal period is one of the most commonly recognized causes of severe, long-term neurologic deficits in children; it is often referred to as cerebral palsy.[40,41] The brain injury that develops is an evolving process that is initiated during the insult and extends into a recovery period, the latter referred to as the "reperfusion phase" of injury. Clinically, it is the latter phase that is amenable to potential intervention(s). Until recently, current management strategies were supportive and not targeted toward the processes of ongoing injury.[42] Thus, it should not be surprising that, despite improvements in perinatal practice during the past several decades, the incidence of cerebral palsy attributed to intrapartum asphyxia has remained essentially unchanged.[40] However, novel exciting strategies aimed at preventing ongoing injury are being clinically evaluated and offer an opportunity for neuroprotection.

The principal pathogenetic mechanism underlying most of the neuropathology attributed to intrapartum hypoxia-ischemia is impaired cerebral blood flow, which is most likely to occur as a consequence of interruption in placental blood flow and gas exchange; it is often referred to as "asphyxia" or severe fetal academia. The latter is defined as a fetal umbilical arterial pH level of 7.00.[40]

At the cellular level, the reduction in cerebral blood flow and oxygen delivery initiates a cascade of deleterious biochemical events. Depletion of oxygen precludes oxidative phosphorylation and results in a switch to anaerobic metabolism, which is an energy-inefficient state resulting in:

1. Rapid depletion of high-energy phosphate reserves including adenosine triphosphate.

2. Accumulation of lactic acid, and

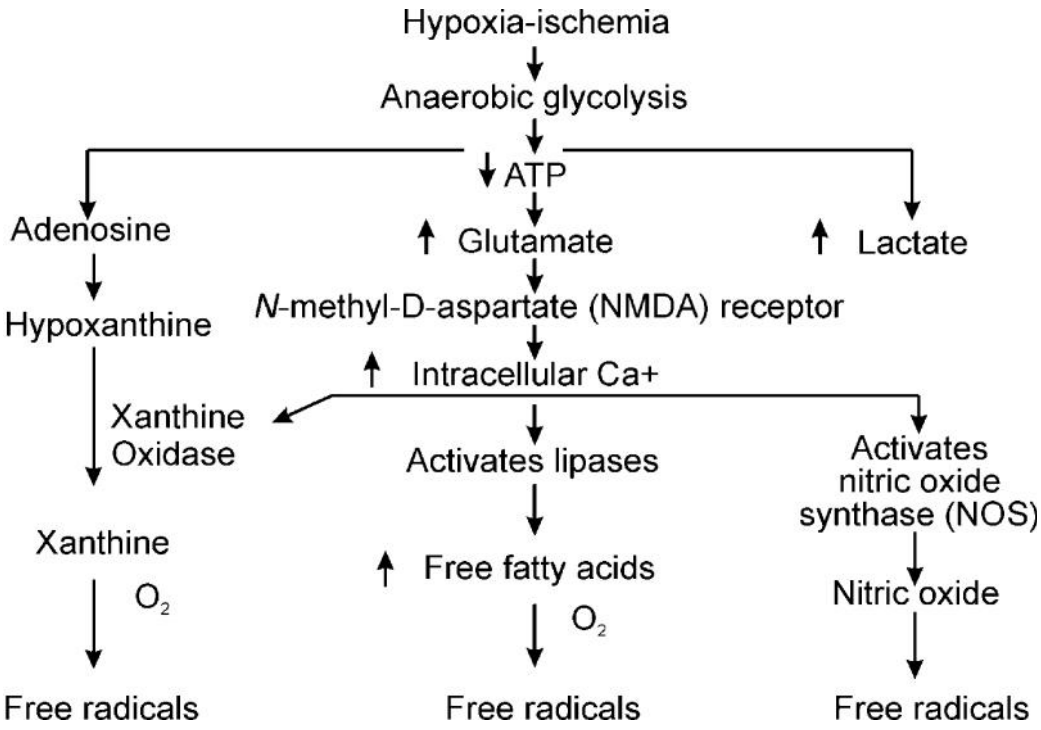
3. The inability to maintain cellular functions.[43]

Transcellular ion-pump failure results in the intracellular accumulation of Na^{+}, Ca^{++}, and water (cytotoxic edema). The membrane depolarization results in a release of excitatory neurotransmitters and specifically glutamate from axon terminals. The glutamate then activates specific cell-surface receptors resulting in an influx of Na^{+} and Ca^{++} into postsynaptic neurons. Within the cytoplasm, there is an accumulation of free fatty acids secondary to increased membrane phospholipid turnover. The fatty acids undergo peroxidation by oxygen free radicals that arise from reductive processes within mitochondria and as byproducts in the synthesis of prostaglandins, xanthine, and uric acid. Ca^{++} ions accumulate within the cytoplasm as a consequence of increased cellular influx as well as decreased efflux across the plasma membrane combined with release from mitochondria and endoplasmic reticulum. In selected neurons, the intracellular calcium induces the production of nitric oxide, a free radical that diffuses into adjacent cells that are susceptible to nitric oxide toxicity. The combined effects of cellular energy failure, acidosis , glutamate release, intracellular Ca^{++} accumulation, lipid peroxidation, and nitric-oxide neurotoxicity serve to disrupt essential components of the cell, which ultimately lead to cell death.[41,44]

NMDA-gated channels have more complex behavior. They have higher conductance, -50 pS, and much slower kinetics. The ion selectivity of NMDA channels is the key to their functions: permeability to Na^{+} and K^{+} causes depolarization and thus excitation of a cell, but their high permeability to Ca^{2+}allows them to influence [Ca^{2+}]. Excess Ca^{2+} can even precipitate the death of a cell.

The gating of NMDA Channels is unusual a normal resting voltage (about-70mV), the channel is clogged by Mg^{2+}, and few ions pass through it; Thus, the NMDA channel is Voltage dependent in addition to being ligand gated;

Activation of the NMDA receptor permits the influx of relatively large amounts of Ca^{2+}along with Na^{+} . When glutamate is in excess in the synaptic cleft, the NMDA receptor-induced influx of Ca^{2+} into neurons is the major basis for the excitotoxic actions of glutamate. At normal membrane potentials, the channel is blocked by extracellular Mg^{2+}. This block is removed only when the neuron containing the receptor is partially depolarized by the activation of adjacent AMPA and kainite receptors



Potential pathways for brain injury after hypoxia-ischemia

Many factors, including the duration or severity of the insult, influence the progression of cellular injury after hypoxia-ischemia.

After resuscitation, which may occur in utero or postnatally in the delivery room, cerebral oxygenation and perfusion are restored. During this recovery phase, the concentrations of phosphorus matabolites and the intracellular pH return to baseline. However, the process of cerebral energy failure recurs from 6 to 48 hours later in a second phase of injury. This phase is characterized by a decrease in the ration of phosphocreatine/inorganic phosphate, with an unchanged intracellular pH and stable cardiorespiratory status, and contributes to additional brain injury.[43,45] In the human infant, the severity of the second energy failure is correlated with adverse neurodevelopmental outcomes at 1 and 4 years.[46] The mechanisms of secondary energy failure may involve mitochondrial dysfunction secondary to extended reactions from primary insults (e.g., calcium influx, excitatory neurotoxicity, oxygen free radicals, nitricoxide formation). Recent evidence suggests that circulatory and endogenous inflammatory cells/mediators also contribute to ongoing brain injury.[47]

MAGNESIUM

Magnesium is the fourth most abundant cation in the body and the second most prevalent intracellular cation. The total body Magnesium content is about 25g or approximately 1 mol, of which about 55% resides in the skeleton. About 45% of magnesium is intracellular. In general, the higher the meta- activity of a cell, the greater is its magnesium content. 80% of cytosolic Magnesium bound to ATP, and Mg ATP is the substrate for numerous enzymes. The nucleus, mitochondria, and endoplasmic Magnesium contain significant amounts of Magnesium.Magnesium is a

cofactor for more than 300 enzymes. Magnesium is most efficiently absorbed from the distal small bowel.

Mechanisms of brain injury

The causes of neuronal death after a hypoxic-ischaemic insult are becoming gradually understood, although our knowledge to date is far from complete and further important information will emerge in this rapidly developing field.

The modern view is that the majority of injury leading to neuronal death occurs after recovery from the initial hypoxic ischaemic insult.

Primary neuronal injury

During the hypoxic-ischaemic insult intracellular energy depletion occurs, and this has a major effect on cell membrane function. Ionic fluxes become deranged as a result of failure to gate neuroreceptors, with the effect of excess sodium, calcium and water entering the cell and leading to cytotoxic neuronal injury and primary neuronal death.

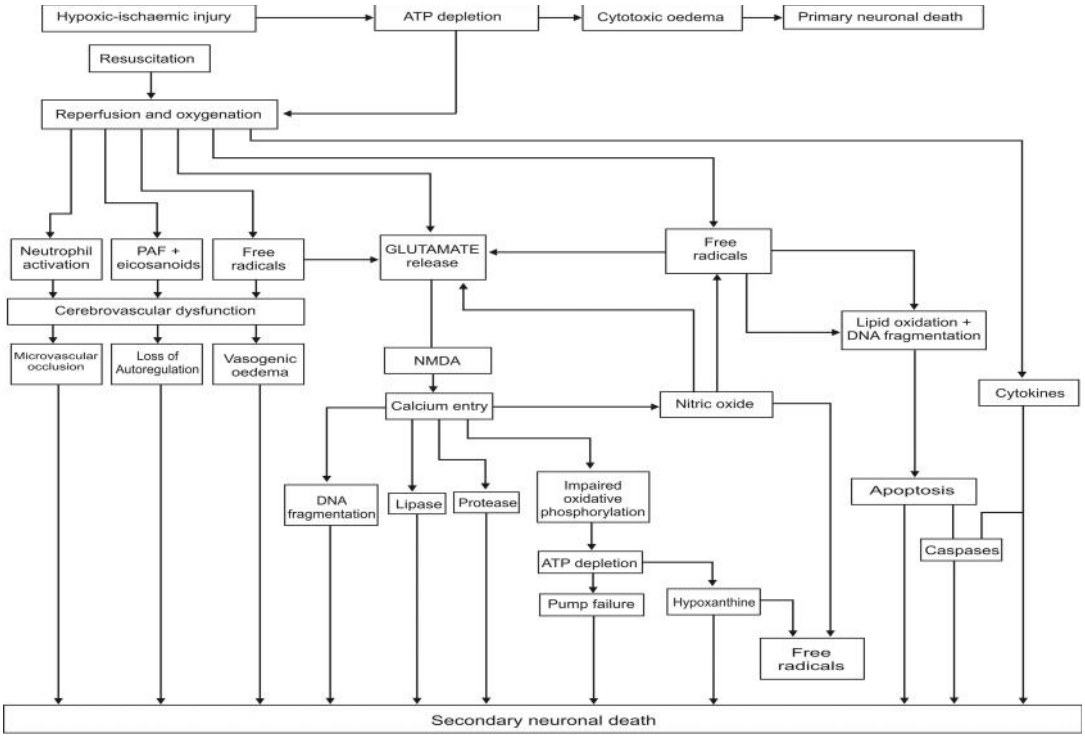
Reperfusion injury

Resuscitation after a hypoxic-ischaemic insult allows reperfusion and oxygenation of compromised tissues, with the initiation of a large number of abnormal biochemical processes. Immediately following resuscitation, a period of hyperperfusion of the brain will occur. This may be in response to accumulation of metabolites, including lactic acid and carbon dioxide, which causes vasodilatation. Following this, vascular tone may increase with increasing reduction of cerebral blood flow, resulting in the so-called no reflow phenomenon.

Reactive oxygen metabolites (free radicals)

With reperfusion, reactive oxygen metabolites are produced, including oxygen free radicals and the more aggressive hydroxyl radicals, and these are generated by the action of the enzyme xanthine oxidase.

Following an asphyxial insult blood flow is reduced to the brain as a result of a number of factors, including insult to the endothelial cell wall with resulting accumulation of white cells and platelets, which infiltrate into the cerebral interstitium, thereby setting off intracellular triggers which may further damage the cell. The clinical effect of this is to cause loss of cerebral autoregulation, reduction in cerebal blood flow and vasogenic oedema.



Simplified schematic representation of the mechanisms involved in secondary neuronal injury following hypoxia-ischaemia.

Nitric oxide:

Nitric oxide is generated in the cell as a result of stimulation of nitric oxide synthase (NOS). This has the effect of generating another reactive metabolite, peroxynitrite, causing lipid peroxidation of intracellular membrances with consequent loss of function.

Excitotoxic injury :

Glutamate acts on the N-methyl-D-aspartate (NMDA) receptor, a postsynaptic ion channel, permitting excessive calcium influx. An increase in intraneuronal calcium initiates activation of lipases, proteases, endonucleases and NOS. This generates further reactive oxygen metabolites, which may in turn increase glutamate release and exacerbate further entry of calcium into the cell, thereby setting up a vicious cycle culminating in neuronal necrosis.

Certain regions of the brain appear to be particularly sensitive to NMDA-related injury, especially the basal ganglia and perirolandic cortex, which are particularly vulnerable in neonates following severe hypoxic-ischaemic insult. Elevated intramitochondrial calcium interfere with function of the structure and may stimulate further reactive oxygen metabolites to be produced.

Apoptosis:

Cell death following hypoxic-ischaemic insult is often due to both necrotic and apoptotic processes with interrelated pathogenesis.

The final apoptotic signal, which causes cell death, appears to be the caspase mechanism. A variety of insults leading to disruption of the mitochondrial membrane

activates caspase-9, which in turn stimulates caspase-3. This undertakes cell execution to complete apoptosis.

With a mean of 1.27 ± 0.15 mmol/l, physiological cerebrospinal fluid (CSF) concentrations are higher than serum concentrations suggesting an active transport through the blood–brain-barrier and blood-CSF-barrier. However, CSF concentrations increase only moderately even after several days of high-dose administration (1.50 ± 0.16 mmol/l at serum levels of 2.14 ± 0.21) indicating a saturation of transport capacity.

Early clinical course of Postasphyxial Encephalopathy:

Although the severity and timing of the intrauterine brain insult is often unclear, retrospective studies have described a characteristic evolution to the clinical picture of HIE in the full-term newborn over the first week after birth. The normal premature infant has a relatively limited range of responses, making these phases of encephalopathy less distinct in the asphyxiated preterm. The early neonatal course of the asphyxiated full-term infant may be discussed in four broad phases:

1) Over the first 12 hours after birth. Infants with mild insults and ultimate injury may have a "hypervigilant" appearance with excessive irritability; however, seizures do not develop. Moderate to severe insults tend to be associated with seizures, and approximately half of these occur within the first 12 hours after birth. Seizures and their manifestations are discussed in more detail later. Infants with severe insults have a markedly depressed sensorium and hypotonia from the first hours after birth.

2) Between 12 and 24 hours after birth. Infants with mild insults may have an apparently normal sensorium. With eyes open but with failure to fix and follow.

Mild degrees of hypotonia may persist. Severely encephalopathic infants tend to have persistent seizures (which may be clinically silent) and declining level of consciousness.

3) Between 24 and 72 hours after birth. Infants with mild insults recover normal levels of alertness and responsiveness and begin feeding. Conversely, severely encephalopathic infants continue to deteriorate and, during this period, may begin to develop prominent brain stem abnormalities, such as ataxic respiration, impaired eye movements, facial weakness, and papillary dysfunction. Severely affected infants are usually unresponsive during this time, with marked hypotonia and in some cases, areflexia, thought to be caused by anterior horn cell injury in the spinal cord

4) Between 72 hours and 7 days after birth. A gradual improvement in mental status and neurologic examination is usually evident; the extent and rate of recovery depend on the initial severity of the insult. In infants surviving severe insults, persistent cranial nerve dysfunction often results in ongoing difficulties with sucking, feeding, and ventilation. During this period, seizures are more easily controlled and often cease. The extent of neurologic recovery by the end of the first week is an important predictor for long-term outcome

Measurement of Total Magnesium

Serum magnesium has been measured by various techniques including photometry, fluorometry, flame emission spectroscopy, and atomic absorption spectrometry (AAS).

Photometric Methods

Calmagite [1-(1-hydroxy-4-methyl-2-phenylazo)-2-naphthol 4- sulfonic acid] Methylthymol blue formazan dye [1,5-bis(3,5-dichloro-2-hydroxyphenyl)-3-formazan carbonitrile] Xylidyl blue [1-azo-2 hydroxy-3-(2,4-dioxanilido)-naphthalene-1- (2-hydroxybenzene)]

Aborption Spectrometry

AAS methods provide greater accuracy and magnesium measurements than do photometric. Methods have been developed with hexokinase enzyme that uses Mg^{2+}-ATP as a substrate. The enzyme-catalyzed reaction is dependent on the concentration of magnesium.

Reference Intervals for Total and Free

(Ionized) Magnesim

Reference intervals for total serum magnesium of 1.7 to 2.4mg/dL or 0.66 to 1.07 mmol/L have been reported.

CONVERSION FACTORS FOR THE UNITS USED TO EXPRESS MAGNESIM

Mmol/L = mEq/L x 0.5 = mg/dl x 0.41

mEq/L = mmol/L x 2 = mg/dL x 0.82

mg/dL = mEq/L x 1.22 = mmol/L x 2.4

INVESTIGATIONS

Blood

Serum glucose, electrolytes, Ca, Mg, ammonia, lactate, pyruvate. Serial acid base study will help in close monitoring of these sick babies.

CSF

Lumbar puncture is also done to rule out infection as chorioamnionitis in the fetus can result in asphyxia.

EEG

Electroencephalography changes provide valuable information regarding the severity. The role of EEG in assessing brain death is not clear. An isoelectric EEG can be seen in patients with neuronal necrosis. Conversely persistent EEG activity has been recorded even with other evidence of brain death.

USG

The anterior fontanelle approach is used to detect injury to the basal ganglia, thalamus and Periventricular Leucomalacia is the initial formation of small echolucent cysts to final Swiss cheese appearance. However, as many as 50% of neurosonograms in neonates with HIE are normal.[48] The presence of hyperechogenic basal ganglia or cystic degeneration of the white matter on sonograms is predictive of a poor outcome.[49]

CT Scan

It provides important information in the diagnosis of diffuse cortical injury in severe selective neuronal necrosis. The value in assessment is evident only several weeks after injury.[3] Computed tomography (CT) is more useful in older children than in neonates. The main reason for its limited utility in neonates is the high water content of the neonatal brain, which reduces contrast between normal and injured tissue. In asphyxiated neonates, CT shows low attenuation in affected grey matter, such as the thalami, basal ganglia, or cerebral cortex,[50] but in general is unable to provide characteristic or prognostic findings.

MRI

Selective cortical neuronal necrosis is shown by hyper intensity of cortex on weighted images followed by development of selective neuronal necrosis. Parasagittal injury is best seen on MRI.[51] Documented patterns include absence of the normal signal intensity in the posterior limb of the internal capsule, bilateral abnormalities within the basal ganglia and thalami, loss of grey/white matter differentiation in the hemispheres, and highlighting of the cerebral cortex.[49,52,53] In addition, abnormalities detected on MRI studies have good predictive value for neurodevelopmental outcome.[49,53]

Magnetic Resonance Spectroscopy

Helps in early delineation of impaired energy metabolism and identification of infants who are candidates for therapy that interrupt events leading to cell death.[51]

Technetium Scan

It is based on an uptake of technetium that crosses a damaged blood brain barrier. This is detected by an external array of gamma detectors thereby giving a coarse image of topographic injury. A technetium scan is valuable in the evaluation of full term infants. The optimal postnatal age for the study is 7 days. Abnormalities usually disappear within 3-4 weeks.[54]

OTHER INVESTIGATIONS

Creatinine kinase (brain specific), Hypoxanthine, Aspartate aminotransferase, Erythropoietin, Endorphin, Lactate, Ascorbic acid and neuron specific enolase may be helpful in evaluating hypoxic damage.[55]

MANAGEMENT

1. Oxygen levels

Oxygen levels have to be kept in normal range by monitoring transcutaneous or arterial PO_2. Hypoxia should be treated by oxygen and /or ventilation. Only minimal handling is recommended. Hyperoxia also causes problems due to free radical production and decrease in cerebral blood flow. Now there is evidence to support the theory that resuscitation of asphyxiated newborn with room air is as effective as using 100% oxygen. Neurologically the infants did not differ from each other.[55] Maintain the blood gases and acid-base status in the physiological ranges including partial pressure of arterial oxygen (P_aO_2), 80-100 mm Hg; partial pressure of arterial carbon dioxide (P_aCO_2), 35-40 mm Hg; and pH, 7.35-7.45.

2. Carbon Dioxide Levels

Carbon Dioxide should be kept in normal range. Hypercapnia causes tissue acidosis and increased cerebral blood flow. More blood flow to uninjured areas with relative ischemia to damaged areas (Steal phenomenon) causes extension of infarct size. Hypocapnia decreases cerebral blood flow.

3. Perfusion

Cerebral perfusion pressure = Mean blood pressure – Intracranial tension

Cerebral Perfusion Pressure (CCP) should be maintained within narrow range. Too little can cause ischemic injury and too much can cause hemorrhage in damaged areas. In asphyxia, cerebral auto regulation is lost. So cerebral perfusion entirely reflects systemic BP in a pressure passive fashion. In asphyxia, a CPP is equal to MBP, central venous pressure (CVP) and MBP should be monitored and maintained as shown in the table. 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 hypovolumia (preload) in babies with asphyxia. Maintain the mean BP above 5 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.

Normal CVP and MBP

Maturity	CVP (mmhg)	MBP (mmhg)
Term	**5-8**	**45-50**
Preterm <1000grams 1000-2000grams	 **3-5** **-**	 **30-35** **35-40**

Crystalloids, colloids and vasopressors have to be used judiciously to maintain CVP, MBP and CPP. Conversely if hypertension develops and persists despite discontinuation of pressors and adequate sedation, the systemic BP should not be further lowered, since it may be required to maintain CPP in the face of elevated ICT.

4. Glucose Levels

Blood glucose level should be kept at 75-100mg/dL range to provide adequate substrate for the brain. Both hyperglycemia and hypoglycemia have been shown to be harmful to brain in asphyxia by different studies. Normal glucose infusion rates of 5-8 mg/kg/min may not be enough to maintain normoglycemia and rates as high as 9-15mg/kg/min may be needed. Glucose infusions should be discontinued slowly to avoid rebound hypoglycemia. In seizures hypoglycemia should be corrected before giving anticonvulsants. Such seizures should not be used for Sarnat staging.[32] 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.

5. Calcium Levels

Calcium level should be maintained in normal range by monitoring serum level. All infants with asphyxia should have the serum calcium levels monitored. Calcium should be provided in a maintenance dose of 4ml/kg/day (of10% calcium gluconate) for 1-2 days.

6. Temperature

The temperature of the newborn should be kept in normal range. Though deep hypothermia as shown to be neuroprotective in animals has not been proved humans.[56] Hypothermia may protect neurons by reducing cerebral metabolic rate, attenuating the release of excitatory amino acids (glutamate, dopamine), ameliorating the ischemia-impaired uptake of glutamate, and lowering the production of toxic nitric oxide and free radicals. Since, in most cases, the hypoxic-ischemic (HI) insult occurs near birth, it is feasible that neuroprotection could be achieved in the first few hours after birth. Accordingly, therapeutic hypothermia, when started within 6 hours of birth, modestly improves the neurologic outcome of full-term infants with moderate HIE and is becoming a standard therapy for this condition (Edwards et al., 2010). Besides the neurological improvement, therapeutic hypothermia was associated with a decreased injury in basal ganglia/thalamus and white matter in MRI scans (Rutherford et al., 2010), confirming the neuroprotective effect of this treatment, as observed in animal models of HIE (Gunn et al., 1997). The therapeutic window of hypothermia coincides with a latent phase, when cerebral energy metabolism returns to normal following perinatal asphyxia. After 6-24hours, this latent phase is followed by a secondary energy failure (Lorek et al., 1994), when there is a correlation between the

degree of derangement of oxidative metabolism and the neurodevelopmental outcome (Martin et al., 1996). Thereby, it has been suggested that irreversible cell death occurs with a certain delay after HIE. However, studies in asphyxiated infants have shown selective head cooling combined with mild systemic hypothermia to be safe, well-tolerated method of reducing cerebral temperature.[57,58]

7. Cerebral edema and fluid management

A simple bedside estimate of ICT can be made in infants by measuring the vertical distance between the anterior fontanelle and heart, measured at the point that the mid portion of the fontanelle flattens as the baby is tited up. Devices applied to the anterior fontanelle provide noninvasive methods for measuring ICT. Normal will be 50 mm H_2O or 5 mmHg. Management of ICT is not important in asphyxia because of following reasons:

1. Cerebral edema and raised ICT are uncommon accompaniments of asphyxia.

2. When present, ICT reflects extensive cerebral necrosis rather than swelling of intact cells. It has uniformly poor prognosis. It peaks at 36-72 hrs after the insult. It is more properly regarded as an effect rather than cause of brain damage.

3. MBP, not intracranial pressure primarily affects cerebral perfusion. Also there is no deterioration in neurological function by EEG or clinical examination at the time of maximum ICT recordings.

4. Infant's patent sutures and open fontanelles are protective to some extent of any acute increase in ICT that might occur. So, current

5. treatment of ICT is restricted to fluid therapy. Avoiding fluid overload can minimize cerebral edema.

8. Control of convulsions

Always look and treat for other specific etiology of seizures (hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia), which may co-exist.

Prophylactic Vs therapeutic anticonvulsants

Prophylactic Phenobarbital at 2 hour to newborn infants with birth asphyxia showed that seizures occurred in 75 percent of both test and control groups with similar neurological outcome and mortality. The only difference was higher incidence of hypotension requiring ionotrope support in prophylactic group.[59]

So at present anticonvulsant are recommended only at onset of symptoms and not prophylactically. Similarly only clinical seizures or changes in blood pressure and heart rate in paralyzed infants need to be treated. Asymptomatic electrical seizures need not be treated, as they are brief, not known to cause damage and the need for high doses anticonvulsants to abolish such activity, which can cause various adverse effects.[60]

Phenobarbitone

It is the drug of choice. It enters the CSF and brain rapidly with high efficiency. Blood level is predictable following intravenous dose. Protein binding is lower in newborns and so free levels are higher. The drug has been reported to have some cerebroprotective effect.

Phenytoin

Phenytoin in high doses in adults has been shown to cause irreversible injury to purkinje cells of cerebellum though not proven in newborns. The main advantage is that it does not cause respiratory depression and sedation in the usual dose.

Diazepam

It is not a preferable drug for maintenance because of extremely rapid redistribution out of brain. When used with phenobarbitone, it carries an increased risk of severe circulatory collapse and respiratory failure. Therapeutic levels are variable and not always less than toxic dose. Vehicle for diazepam is sodium benzoate, which can displace bilirubin from albumin predisposing to kernicterus.

Suggested protocol for acute seizures [56]

After treating hypoglycemia and hypocalcemia, Phenobarbital is given IV in a loading dose of 15-20 mg/kg 10-15 minutes with careful monitoring of blood pressure and respiration. A dose or 20 mg/kg achieves a blood level of 20 mcg/ml, which is needed to achieve anticonvulsant effect. If seizures are not controlled, administer additional doses of 5 mg/kg every 15 minutes till seizures are controlled or a total dose of 40mg/kg is reached. Total dose in excess of 40mg/kg does not provide additional anticonvulsant effect. In severely asphjyxiated infant with hepatic or renal dysfunction, higher blood levels are reached and last longer with 40mg/kg dose resulting in sedation and hypotension for several days. Hence after first 20mg/kg dose, some clinicians go for 20mg/kg phenytoin with cardiac monitoring. If still there is no response, I.V. lorazepam is given at dose of 0.05- 0.1 IV-g/kg as often as needed. It is better to use phenytoin when the baby is comatosed or has respiratory

depression. A combination of phenytoin with phenobarbitone often controls convulsions better with lesser side effects. Other drugs used for acute seizures are primidone, lidocaine, thiopentone, paraldehyde and valproate where experience in newborns is lacking. Once levels of conventional anticonvulsants are maximized to 40mcg/ml for phenobarbitone and 20 mcg/ml phenytoin, there is little reason to eliminate every twitch.

Maintenance therapy

Maintenance therapy is with phenobarbitone at dose of 3-5 mg/kg day in 2 divided doses IV or orally and/or phenytoin at 5-8 mg/kg/day in 2 divided doses IV. Oral absorption of phenytoin is poor. When infant's condition is stable for 3-4 days, anticonvulsants are weaned of gradually.

Duration of treatment and indications for stopping anticonvulsant:

Optimum duration of therapy relates to the likelihood of recurrence of seizures if the drugs are discontinued. The three main determinants include neurological status, cause of seizures and EEG. If neurological examination is abnormal, 50% will have recurrence, while if interictal EEG is abnormal it is 40%. The recurrence is 20-30% with asphyxia and 100% cortical dysgenesis. Metabolic seizures have the lowest recurrence rates.

OTHER SYSTEM MANAGEMENT

Management of cardiac effects

Adequate ventilation with correction of hypoxemia acidosis and hypoglycemia can reduce myocardial damage. Volume overload must be avoided. Diuretics may be ineffective if there is concomitant renal failure. If there is cardiac collapse, ionotrope

drugs like dopamine and dobutamine have to be started. Epinephrine should be avoided as it causes vasoconstriction and fall in perfusion and acidosis. Some infants in great distress may require afterload reduction with a peripheral beta agonist like isoproteronol or peripheral alph-blocker like phentolamine, tolazoline or nitroprusside.[56]

Management of renal effects

Two main problems are acute tubular Necrosis (ATN) and. Syndrome of inappropriate antidiuretic hormone secretion (SIADH), which are managed mainly by fluid restriction. Oliguria must not be attributed to SIADH or ATN unless prerenal etiologies such as hypovolemia or vasodilation have been ruled out. Dopamine at 1.25-2.5mcg/kg/min may aid renal blood flow. Dialysis is the treatment for severe cases, but not offered to any babies because of high mortality associated with such cases.[56]

Gastrointestinal effects

There is increased risk for bowel ischemia and necrotizing enterocolitis. So infants with asphyxia must not be fed for 2-3 days or till good bowel sounds are heard and stools are negative for blood or reducing substance.[56]

Hepatic effects

Since there may be bleeding due to hepatic dysfunction clotting factors and fresh frozen plasma may be given. Blood sugar should be maintained at 75-100 mg/dl and drugs metabolized by liver should be avoided.[56]

Pulmonary effects

Adequate oxygenation and ventilation with possibly mild alkalinization may be helpful. Method of ventiliation is hyaline membrane disease, primary pulmonary hypertension of newborn or meconium aspiration syndrome. High frequency ventilation and ECMO can be tried in selected cases.[61]

POTENTIAL NEW THERAPIES OF CEREBROPROTECTION

It was very difficult to predict during the neonatal period which neonates will suffer the most profound damage after an insult to the central nervous system, since more than 30 percent of neonates presenting with moderate encephalopathy have normal outcome. The insight into the biochemical and cellular mechanisms of neuronal injury with perinatal HIE helps to provide interventions to interrupt those deleterious cascades, principally focusing on the potential effects of free radical scavengers, such as N-acetylcysteine (NAC) and allopurinol, magnesium, glutamate receptor blockers, erythropoietin (Epo), and hypothermia. NAC is a free radical scavenger and has been demonstrated to minimize hypoxia-ischemia induced brain injury in various acute models[62,63,64]. Combination therapy of NAC and systemic hypothermia improves infarct volume, myelin expression after focal HI injury[62].

Oxygen free radical inhibitors and scavengers

Antioxidant enzymes, superoxide dismutase and catalase conjugated to polyethylene glycol have prolonged half life and improved penetration into blood brain barrier, but protective only if administered many hours before hypoxic insult.

Xanthine oxidase inhibitors

Allopurinol and oxypurinol protect immature rats from hypoxic damage even when administered early during the recovery phase after resuscitation. In hypoxia

ATP is degraded forming adenosine, which is metabolized with the help of xanthine oxidase to uric acid releasing superoxide and hydrogen peroxide as side products. So inhibition of xanthine oxidase decreases free radical production.[65,66]

Elimination of free iron

Iron has the ability to transfer electrons and catalyze formation of more reactive species – hydroxyl radicals and other iron-oxygen compounds like ferryl and perferryl ions. So depletion of dietary iron or chelation with desferrioxamine is tried in experimental animals.[67]

Prevention of excess nitric oxide formation

NO is produced by endothelial cells and microglial cells in response to asphyxia. Superoxide and NO combine to form peroxynitrite, which decomposes releasing oxidants. Inhibition of NO synthesis with L-NAME- (Nitro L arginine methyl ester) has been tried. It prevents secondary brain injury by suppression of NO production during recovery. But inhibition during hypoxic insult be deleterious.

Vitamin E (alpha-tocopherol)

Membrane bound chain breaking antioxidant prevents chain elongation in free radical damage.

Lazeroids-non-glucocorticoid 21 aminosteroid

Prevents iron dependent lipid peroxidation by scavenging peroxyl radicals.[68]

Indomethacin-cyclooxygenase and phospholipase inhibitors

Ameliorate ischemic brain damage at least in adult animals and substantially reduce free radical generation during reperfusion.

Excitatory amino acid antagonists

Agents that would inhibit glutamate release from nerve terminal (e.g. baclofen) or block its postsynaptic action (NMDA and AMPA receptors or ion channel e.g. phencyclidine, ketamine, MK-801)[69] reduce hypoxic damage in adult animals even when administered up to 24 hours after the metabolic insult. NMDA and AMPA receptor antagonists are the most potent drugs available to ameliorate the devastating effects of hypoxia.

Magnesium sulphate

Retrospective study has suggested that premature babies whose mothers received magnesium sulphate for the treatment of pre eclampsia or as tocolytic agents are less likely to develop cerebral palsy compared with those not exposed to the drug. Divalent magnesium ion is glutamate receptor antagonist, which blocks neuronal influx of calcium ions.[3]

Calcium channel blockers

Calcium is an intracellular second messenger, which causes hypoxic damage by multiple mechanisms. Calcium channel blockers, which cross the blood brain barrier like flunarizine and nimodipine,, are tried. But the neuroprotective effect is not impressive.[3]

Other drugs

Monosialogangliosides are important constituent of nerve cell membrane. It gives neuroprotection by incorporation into cell membrane.

Growth factors

Nerve Growth Factor has been shown to reduce severity of hypoxic damage in immature rat. The neuroprotective effect of exogenously administered Erythropoietin has received much attention for ischemic disease, and promising data are emerging for the newborn.

Glucocorticoids

Dexamethasone given immediately before hypoxic insult does not give protection. But if administered >24 hrs before insult, there is improved neuronal outcome.

Erythropoietin

Epo, the major haemopoietic growth factor, is now considered to have beneficial effects in various nervous system disorders based on the effects of prevention of metabolic compromise neuronal and vascular degeneration and inflammatory cell activation[70].

Neural stem/progenitor cell transplantation in HIE

When transplanted into the HI brain, NSPC migrate long distances in direction to areas of neural damage. Even when injected in the contralateral hemisphere, NSCP are able to migrate through the interhemispheric comissures toward the damaged hemisphere (Imitola et al., 2004; Park et al.,2006).

Mesenchymal stem/progenitor cell transplantation in HIE

MSC transplantation could be used as a promising new strategy to reduce neuronal death, promote brain plasticity and regeneration and modulate inflammation

after HIE. However, it is still necessary to define the best source of MSC, the therapeutic window, the delivery route and the cell dose, before this therapy can be tested in clinical trials.

NON-PHARMACOLOGICAL INTERVENTIONS

Hypo / Hyperglycemia

Blood glucose level of >600mg/dL is shown to protect the brain. Similarly prolonged fasting induced hypoglycemia (>12hrs) has been shown to be neuroprotective.

Hypothermia

Preliminary results of two randomized clinical trails of either, systemic cooling or selective head cooling in encephalopathic neonates suggest, that moderate hypothermia is safe in the high risk newborn. In at least one study, newborns with moderate encephalopathy had better neurodevelopmental outcomes at 18 months than did newborns in the normothermic group.[71]

Hypoxic Preconditioning

Immature rats subjected to cerebral hypoxia sustain less damage if exposed to hypoxia alone compared to animals not, exposed previously to hypoxia. The mechanism is by induction of genes or proteins that influence metabolic events during insult or reperfusion.

Potential Alternatives:

Most research efforts in neonatal neurology are currently targeted to neuroprotective strategies, but another concept is slowly emerging from the adult

stroke literature. In adults, neurorestorative therapies are currently being developed to treat ischemic brain injury, including cerebral vasculature-based therapy combined with neuroprotection[93] as the more "conventional" strategies (antiapoptosis, anticalcium, anti-inflammation, and antioxidative injury) have been disappointingly ineffective in adult clinical trials. These neurorestorative therapies target the neurovascular unit, composed of functionally integrated cellular (including brain endothelial cells, astrocytes, pericytes and smooth muscle cells, neural stem cells, oligodendrocytes, and neurons) and acellular elements that form the basement membrane[94]. Thus, they lead to enhancement of restorative events, such as endogenous neurogenesis, angiogenesis, axonal sprouting, and synaptogenesis in the ischemic brain, explaining the potential for stimulation of brain plasticity and improvement in functional recovery[95,96].

In adult models of stroke, these therapies have been shown to activate these processes and successfully reduce the size of the infarcted areas[97,98] and are now being actively tested in human patients. The immature brain of a newborn is not simply a "small adult brain," and the mechanisms underlying neonatal HIE is certainly very unique compared to the ones underlying adult stroke[99]. However, evidence is growing in the literature that such a systemic approach might also be useful to better treat neonatal brain injury. One such potential neurorestorative drug in newborns is erythropoietin, which has a recognized role in promoting neural regeneration and neurovascular remodeling[100].

A randomized controlled clinical trial is currently ongoing in human newborns to assess its efficiency (i.e., "neonatal erythropoietin in asphyxiated term newborns," ClinicalTrials.gov Identifier: NCT00719407). Another promising alternative

treatment of neonatal HIE utilizes cord blood and mesenchymal stem cells to replace neurons lost due to brain injury, as well as activate endogenous stem cells, and release growth factors, thus minimizing brain damage and promoting restoration[101,102].

PROGNOSIS OF PERINATAL ASPHYXIA

The degree of asphyxia necessary to cause permanent brain damage in experimental animals is quite close to that which causes death (>25 minutes of total asphyxia). Survival with brain damage is actually uncommon in this model. The extremes of death or intact survival are the most likely outcome. Likewise in humans, birth asphyxia severe enough to damage fetal brain usually kills before or soon after birth, the remainders survive and are normal. The only groups with significant neurological impairment are those who were severely asphyxiated yet, narrowly escaped death. Any infant severely asphyxiated to result in neurological sequelae would have other organ system affected Full term asphyxiated infants have mortality of 10-20% and neurological sequelae in survivors will be 20-45% (40% mild, 60& severe).

With in the first two weeks, it is very difficult to offer a prognosis because the present methods of prognostication are very unreliable.

Unfavourable signs are:

1. Severe prolonged asphyxia
2. Sarnat stage III encephalopathy
3. Multi Organ system involvement
4. Elevated intracranial pressure more than 10mmHg
5. Persistence of abnormal neurological signs at discharge especially absence of moro reflex.

6. Persistence of extensive hypo densities (cystic encephalomalacia) on CT scan) at least 4 weeks after the insult.
7. Abnormalities on brain scan and
8. Persistent oliguria less than 1ml/kg/hour for the first 36 hours of life.[3]

LONG TERM OUTCOME OF INFANTS WITH PERINATAL ASPHYXIA

Long term neurodevelopmental outcome [72, 73, 74]

The characteristic long term sequelae of post asphyxia brain injury include a triad of features cerebral palsy, mental retardation and epilepsy with varying degrees of subtle behavioral and developmental dysfunction in areas of language, fine motor co-ordination, socio-emotional competence and school learning. It can also cause visual and auditory handicap. The longterm sequelae is more severe in term that preterm babies. The major sequelae include motor disabilities, mental retardation, learning and visual impairment and seizure disorders.

Motor disabilities

The characteristic form of cerebral palsy in a term asphyxiated neonate is spastic quadriplegia and chorioathetoid cerebral palsy due to involvement of cerebral cortex and basal ganglia. The upper limbs are usually more affected than lower limbs. Lower cranial nerve involvement may manifest as sucking swallowing problems and this can occur both in term and preterm neonates.

Visual impairments

It occurs both in preterm and term asphyxiated neonates. In the preterm it is because of damage to optic radiation in the Perventricular region and in the term neonate it is due to the damage to the visual cortex.

Hearing impairment

It can in both term and preterm neonates and is due to damage to the cochlear nuclei and to the auditory pathway. The incidence of hearing impairment in a preterm asphyxiated neonate may be as high as 25%.[74] The incidence of major motor disabilities in asphyxiated neonates very depending on the severity of asphyxia. In moderate to severe encephalopathy the incidence of neurodevelopmental sequelae varies from 16% to 28%.[73, 75, 76] It is however important to note in studies looking at etiology of cerebral palsy-asphyxia is a cause of cerebral palsy only in 10-25% of cases.[72, 77, 78, 79]

Mental retardation-cognitive and learning disabilities[73, 74]

Moderate to severe mental retardation may be seen both in term and preterm asphyxiated neonates. Even if mental retardation is not there, impaired cognitive function in the form of learning disabilities is often seen in moderate and severely asphyxiated neonates. Learning functions specifically affected are language skills, mathematics and visual-spatial abilities. In follow up studies it hs been shown that cognitive abilities are comparable to normal neonates in mildly asphyxiated babies, but impaired in moderate to severe asphyxia.[73,74,75]

Growth and physical maturation[73]

Physical growth in terms of weight and length is usually not affected in term asphyxiated neonates. However microcephaly may be a problem in severely asphyxiated neonates.[80] Some follow-up studies have shown advanced sexual maturity in asphyxiated neonates.

A significant number of neonates with perinatal asphyxia have long term sequelae. Those with mild asphyxia do not have any sequelae. Those with severe asphyxia have a near 100% risk of long-term sequelae. Diagnostic tests such as EEG, CT scan and MRI do help to a certain extent in predicting long-term outcome. It is however important to remember that no single clinical or diagnostic tool can predict long term outcome. Close follow up and involvement of these high risk neonates in the developmental program from the beginning could help in providing support to the families and in decreasing severity of morbidity.[81]

METHODOLOGY

SOURCE OF DATA:

Term neonates (gestational age of more than 37 to less than 42 completed weeks) with birth asphyxia delivered in

The study was conducted from November 2012 to March 2014.

METHORD OF DATA COLLECTION:

After taking the informed consent from the parents or guardian and fulfilling inclusion and exclusion criteria, patients was included in the study

Inclusion criteria

All single term neonates with Apgar score of 3 or less at 1minute and 6 or less at 5 minutes. (Term neonates with perinatal asphyxia as defined by WHO and NNPD)

Exclusion Criteria

1. All Preterm and post term neonates.
2. Neonates with congenital malformations.
3. Neonates with meconium stained amniotic fluid.
4. Patients whose mothers received magnesium sulfate, pethidine, phenobarbitone or other drugs likely to influence the Apgar Score.

METHOD OF DATA COLLECTION:

Randomization of the study was done by; babies delivered on odd dates of a month will be taken as case group and babies delivered on even dates of a month werebe taken as control group. ie a baby delivered on dates like 1,3,5,7 are included in case group and baby delivered on dates like 2,4,6,8, were be considered as control group. A day was considered from 12AM to 11.59PM.

As soon as the baby is admitted to NICU, the details were be entered in a predesigned proforma. This includes history regarding antenatal risk factors for perinatal asphyxia like age of mother, history of pregnancy induced hypertension, anemia, bleeding, infection and systemic disease. Intrapartum factors like mode of delivery, history of prolonged rupture of membrane, meconium stained amniotic fluid, malpresentation and cord prolapse were also entered.

The examination findings including vital signs and detailed anthropometry were recorded and a complete examination of central nervous system, Respiratory system, Cardio vascular system and Gastro-intestinal system was done and recorded in detail.

Case group had received Magnesium sulfate infusion at 250 mg/kg per dose (in 20 mL of 5% dextrose solution) over 1 hour within first hour of birth, and 2 additional doses 125 mg/kg per dose (in 20 mL of 5% dextrose solution) over 1 hour at intervals of 24 hours. This extra fluid was considered along with total daily fluid maintenance dose of the neonates. The neonates of the control group were not received any proposed Magnesium supplementation. Further neonates of both groups were treated as per the routine NICU treatment protocol for birth asphyxia.

Clinical assessments include assessments of the neurologic status twice daily for the first 10 days of life using Sarnat and Sarnat classification of Hypoxic-Ischemic Encephalopathy (HIE) into Stage I, Stage II or Stage III.

Parameters like type of respiratory support needed, the presence of seizures, the time for establishment of full oral feedings, duration of stay in hospital. The assessment of the child was done in NICU and will be continued in wards if the child is transferred for mother side admission.

The symptoms of hypermagnesemia in neonates like lethargy, vomiting, Impaired breathing, decreased respiratory rate, hypotension, bradycardia, arrhythmia and asystole, decreased /absent deep tendon reflexes are monitored. Complications associated with *Cardiac system* like bradycardia/tachycardia, rhythm abnormalities, appearance of murmurs; *Renal system* like Hematuria, oliguria, renal failure; *Respiratory system* like duration of oxygen dependence, respiratory failure, *Gastrointestinal system* like Necrotizing enterocolitis, feed intolerance; Hematological abnormalities like Thrombocytopenia, hyperbilirubinemia, coagulation abnormalities; *Metabolic disturbances* like Acidosis, hypoglycemia, hypocalcemia, hyponatremia were monitored in both the study groups.

Laboratory assessments include serum Magnesium estimation on admission in NICU and then on 12, 24, 48 and 72 hours of life was done in both groups. Routine NICU protocol investigations for birth asphyxia will also be done.

Serum magnesium is measured using Calmagite Method**.**

PRICCIPLE: Magnesium combines with Calmagite in an alkaline medium to form a red coloured complex. Interference of calcium and proteins is eliminated by the

addition of specific chelating agents and detergents. Intensity of the colour formed is directly proportional to the amount of magnesium present in the sample.

Magnesium + Calmagite ⟶ **Red coloured complex**

PROCEDURE

Wavelength / filter : 510 nm (Hg 546 nm)/Green

Temperature : Room Temperature

Light path : 1 cm

DATA ANALYSIS

Determination of Sample Size :

Sample size= 30 neonates in each group

The sample size for the comparative study of each group may be determined using the formula[103] with permissible error of 0.054

$$\mathbf{n} = \frac{[Z_{\sim/2} \pm]^2}{E^2}$$

$$= \frac{3.8416 \text{ X } 0.151066^2}{0.054^2}$$

$$= \mathbf{30}$$

Z = Standard normal variable

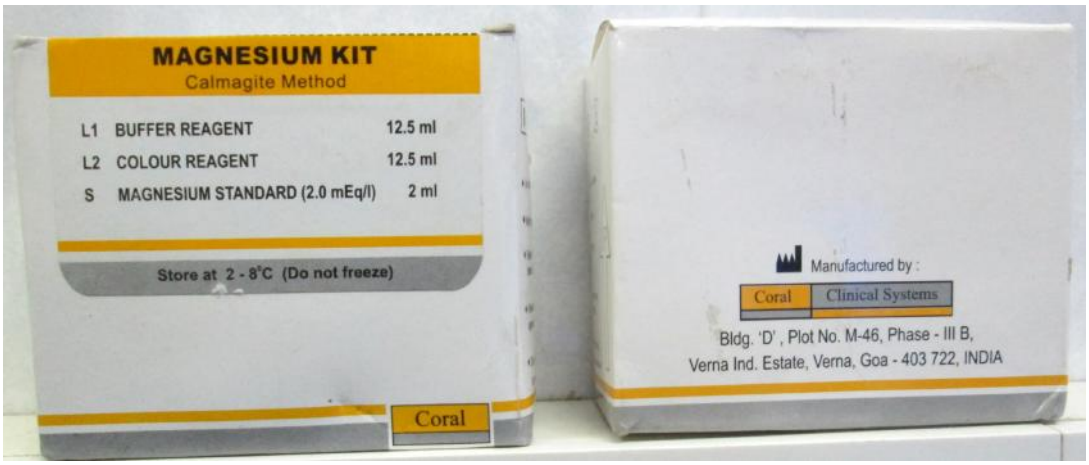
E = Permissible error

Here $[Z_{\alpha/2}]^2 = [1.96]^2 = 3.8416$, the theoretical value of z statistic at 5 % level of significance

σ^2= assumed as standard value from a previous study[104]

$= (0.151066)^2$

Magnesium Reagent and Magnesium Sulphate ampoules



Magnesium Kit

OBSERVATIONS AND RESULTS:-

The duration of study period was from November, 2012 to March, 2014.

85 patients of birth asphyxia were enrolled in the study of which 45 cases and 40 control group.

Total number of deliveries during the study period was 2537

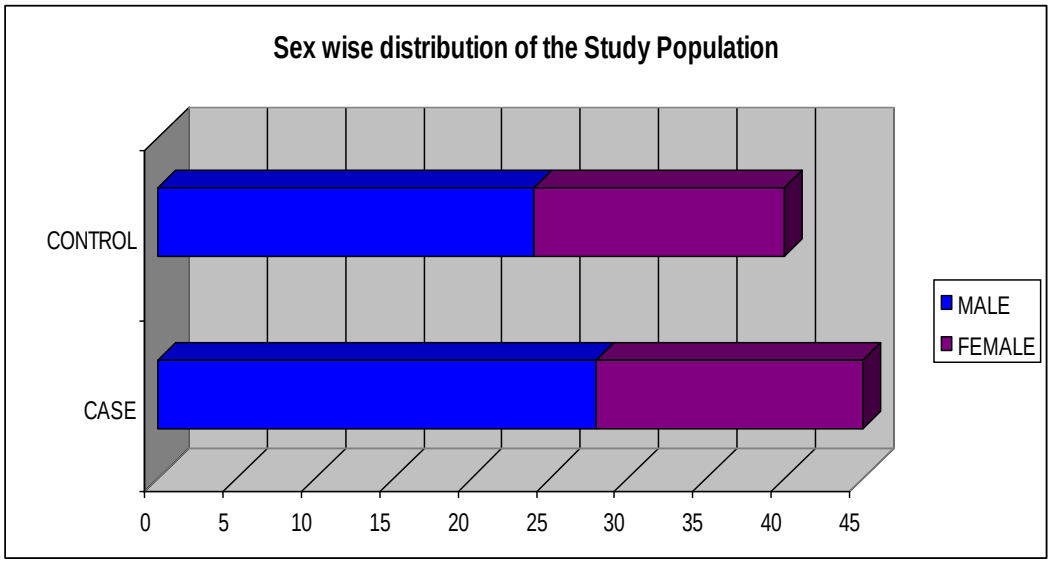
Incidence of Birth Asphyxia during the present study period was 3.35

Statistical analysis was done using significance of serum Magnesium and outcome. This was analysed using **t-test** in the present study.

The observations are as follows:-

Table 1. Gender distribution of the Study Population

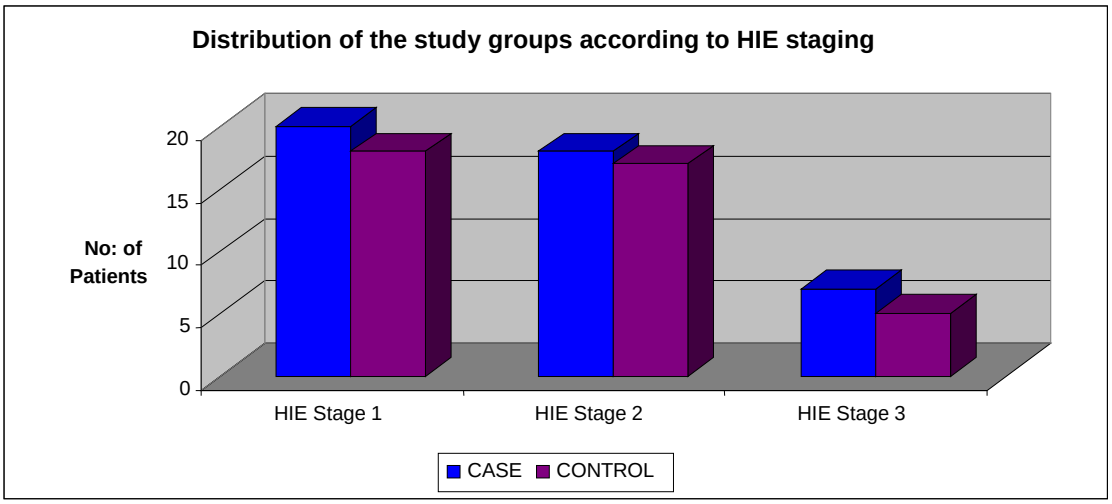
SEX	CASE	CONTROL	TOTAL
MALE	28(33%)	24(28%)	52(61%)
FEMALE	17(20%)	16(19%)	33(39%)
TOTAL	45(53%)	40(47%)	100(100%)



There were 52 (61%) male babies in the total study population. In the study population, case group comprised of 45(53%) babies. Male neonates were more in both the study group.

Table 2. Distribution of study groups according to Sarnet and Sarnet HIE classification.

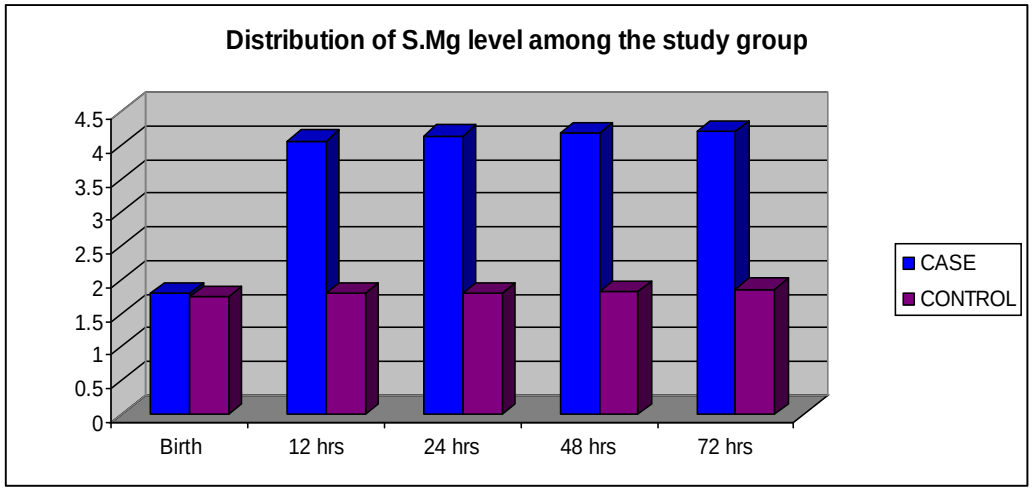
	CASE	CONTROL	Total
HIE Stage 1	20(24%)	18(21%)	38 (45%)
HIE Stage 2	18(21%)	17(20%)	35 (41%)
HIE Stage 3	7(8%)	5(6%)	12 (14%)
TOTAL	45(53%)	40(47%)	85 (100%)



38(45%) patients had Stage 1 HIE, 35(41%) patients had Stage 2 HIE and 12(14%) patients had Stage 3 HIE. Most number of patients came in HIE stage 1 group, 20(24%) patients. Least number of patients were in HIE stage 3 control group, 5(6%) patients.

Table 3. Distribution of mean Serum Magnesium level among the study groups

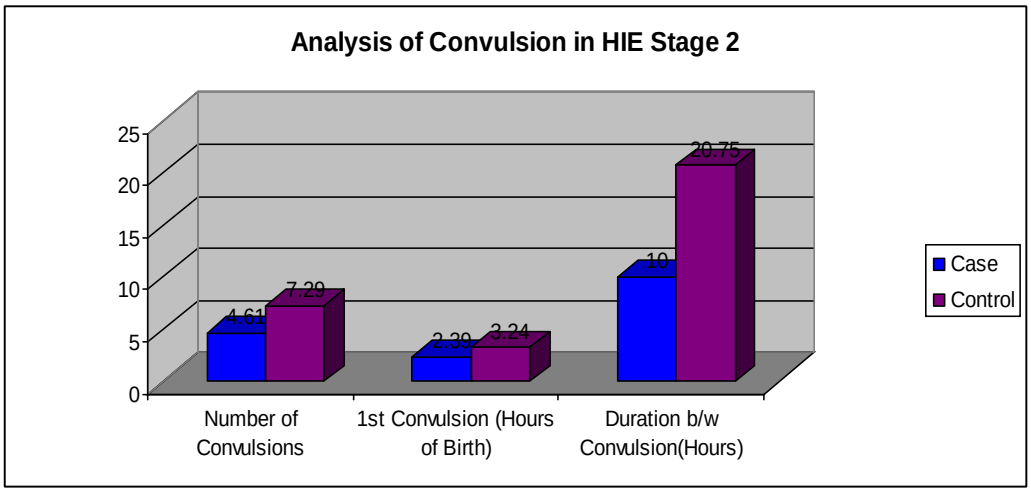
Hours of life	S.Magnesium (mg/dl)		*p*-value	
	Case	Control		
Birth	1.795	1.74	>0.05	Not Significant
12 hours	4.062	1.801	<0.05	Significant
24 hours	4.137	1.797	<0.05	Significant
48 hours	4.172	1.824	<0.05	Significant
72 hours	4.202	1.857	<0.05	Significant



Mean Serum Magnesium level was lowest during birth (Case-1.795 mg/dl; Control-1.740 mg/dl). Magnesium levels were 4.062 mg/dl, 4.137 mg/dl, 4.172mg/dl, 4.202m/dlin cases during 12, 24, 48 and 72 hours of life respectively. All the serum Magnesium values in the cases were in the neuroproctective range during the 1st 72 hours of life.

Table 4: Analysis of Convulsion in HIE Stage -2

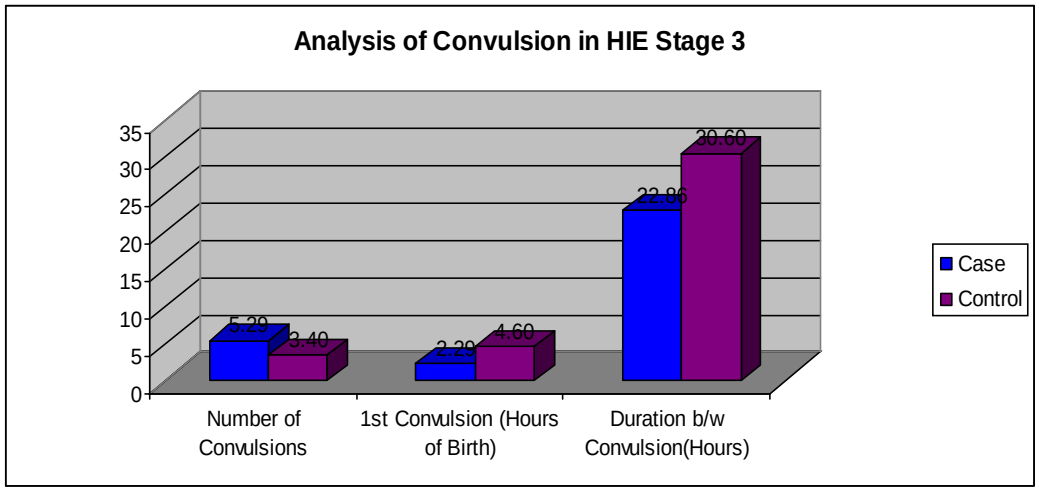
MEAN DURATION	CASE	CONTROL	p- value	
Number of Convulsion	**4.61**	**7.29**	**<0.05**	**Significant**
1st Convulsion (Hours of Life)	**2.39**	**3.24**	**>0.05**	**Not Significant**
Duration (Hours)	**10**	**20.75**	**<0.05**	**Significant**



There was significant reduction in number of convulsions and interval between 1st & last convulsion among the two groups. There was no significant difference in time of presentation of 1st episode of convulsion among the two groups.

Table 5: Analysis of Convulsion in HIE Stage 3

MEAN DURATION	CASE	CONTROL	*p*- value	
Number of Convulsion	**5.29**	**3.40**	**>0.05**	**Not Significant**
1st Convulsion (Hours of life)	**2.29**	**4.60**	**<0.05**	**Significant**
Duration (Hours)	**22.86**	**30.60**	**>0.05**	**Not Significant**



There was significant reduction in time of presentation of 1st episode of convulsion among the two groups. There was no significant difference in number of convulsions and interval between 1st & last convulsion among the two groups.

Distribution of outcome analysis

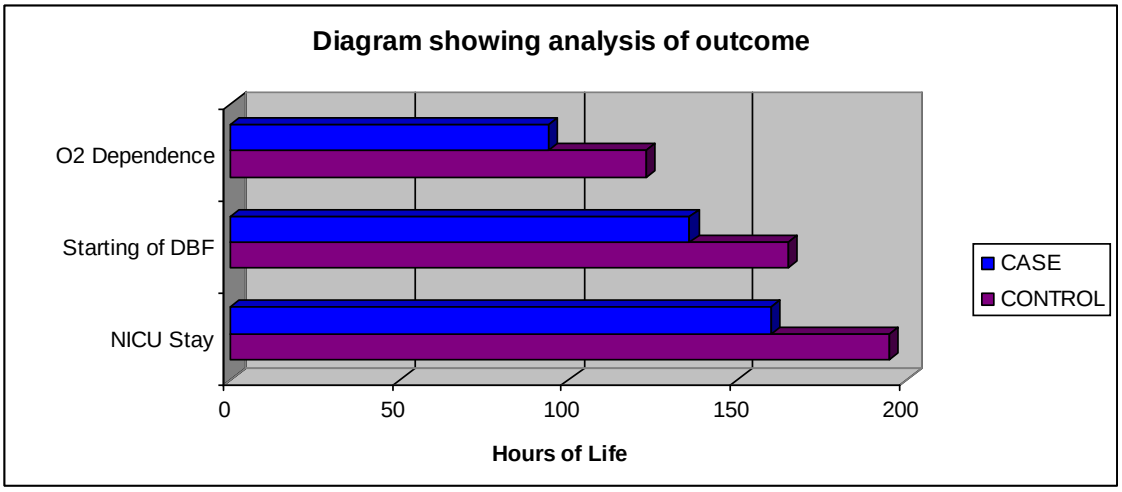


Table 6: Distribution of outcome analysis

Mean Duration	CASE (Hours of Life)	CONTROL (Hours of Life)	P-Value	
O_2 Dependence	94	123	0.00048511	Significant
Starting of DBF	136	165	0.000160049	Significant
NICU Stay	160	195	0.007867336	Significant

There was significant difference among the two groups in

1. **Duration of Oxygen supplementation**
2. **Initiation of DBF**
3. **Duration of NICU stay**

Analysis of complications

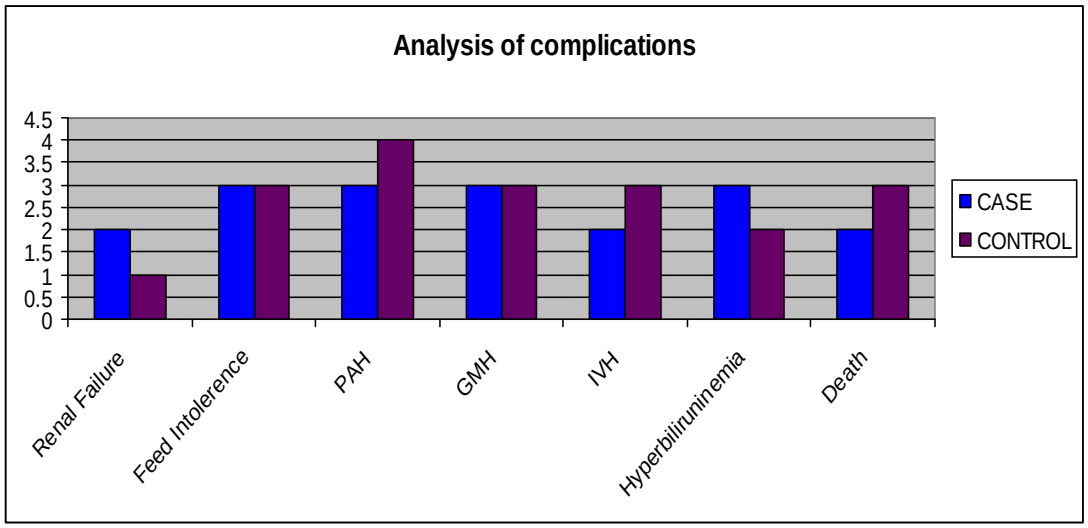


Table7: Analysis of complications

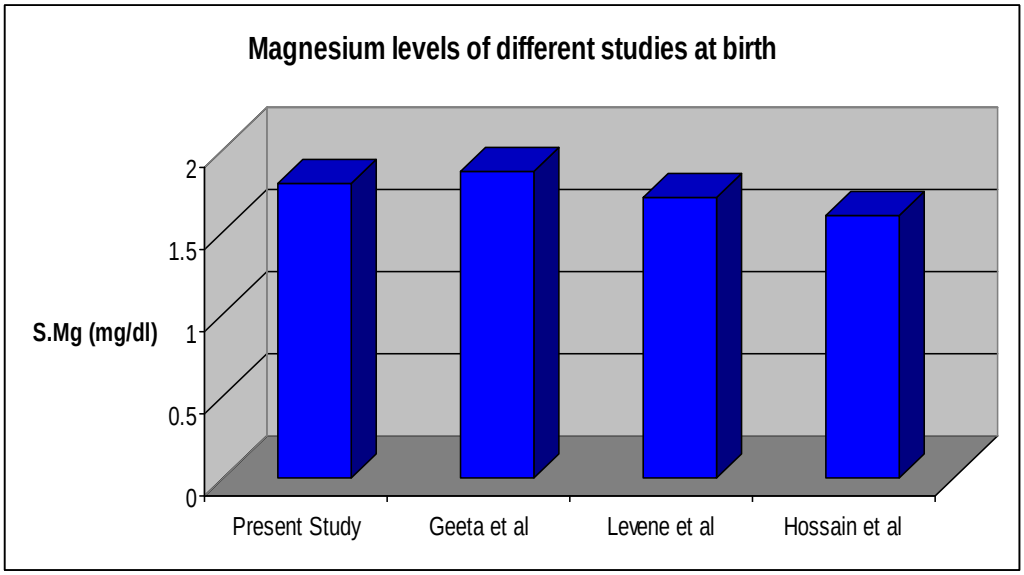
	CASE	CONTROL	Total
Renal Failure	**2**	**1**	**3**
Feed Intolerence	**3**	**3**	**6**
PAH	**3**	**4**	**7**
GMH	**3**	**3**	**6**
IVH	**2**	**3**	**5**
Hyperbilirubinemia	**3**	**2**	**5**
Death	**2**	**3**	**5**

There was no significant difference in the incidence of complications of birth asphyxia.

DISCUSSION

Data from National Neonatal Perinatal database suggests that birth asphyxia contributes to almost 20% of neonatal deaths in India.[6] 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. “Failure to initiate or sustain respiration after birth” is defined as criteria for the diagnosis of asphyxia by WHO.[7]

In our study, the case and control groups had no differences in gestational age, birth weight, gender, mode and place of delivery, parity, antenatal checkup, liquor colour and hypoxic-ischemic encephalopathy (HIE) staging and mean age of intervention between the experimental and controlled groups. The serum magnesium levels at birth were 1.740 (±0.286) mg/dl and 1.795(±0.237) mg/dl in the control and study group respectively. The normal reported values for serum Mg in neonates on day 1 of life are 1.8(±0.15) mg/dl.[106] Geeta *et al* , Levene *et al* and Hossain *et al* reported similar ‘0’ hour serum Mg levels 1.867 mg/dl, 1.704mg/dl and 1.6 mg/dl respectively in babies with severe birth asphyxia.[107, 108, 109] The values obtained in the present study are comparable to these. This is possibly why the Mg levels at birth in the babies with birth asphyxia were not different from those reported in normal neonates.

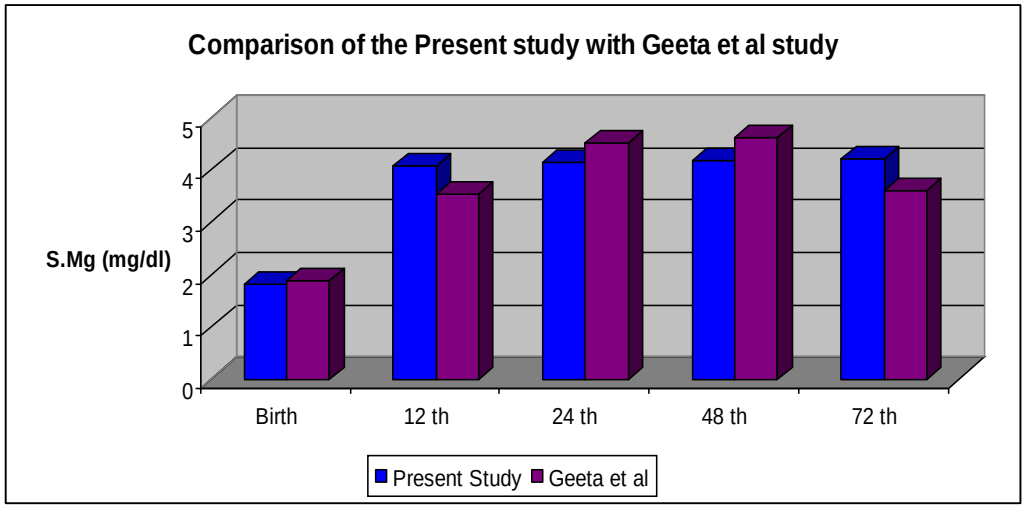


We used 3 doses of Mg –250 mg/kg given within an hour of birth, followed by 125 mg/kg given at 24 and 48 hours of life. The serum Mg levels obtained were between 4.062 (±0.31) mg/dl and 4.062 (±0.22) mg/dl. Geeta *et al* also used the same doseage and serum Magnesium were between 3.523 mg/dl and 4.598 mg/dl. Levene *et al* also used a single dosage of 250 mg/kg. The 12 hour value was 4.062 mg/dl which is similar to that reported by both the studies. 24-hour value was higher at 4.172 mg/dl as similar to Levene *et al* because of an additional dose of 125 mg/kg of Mg, which was administered at 24 hours.

The normal serum Mg levels being 1.8mg/dl to 2.5 mg/dl. Serum Magnesium levels between 3- 5 mg/dl may be expected to be neuroprotective. With the dosage schedule used in the present study, Serum Mg levels obtained were in the range of 4.062- 4.202 mg/dl over a period of 72 hours. The Mg levels reached were therefore in the neuroprotective range. Secondary neuronal injury to the post asphyxial neonatal brain can occur over a period that may last as

Hours of Life	Serum Magnesium (mg/dl)			
	Present Study	**Geeta *et al***	**Levene *et al***	**Hossain e*t al***
Birth	**1.795**	**1.867**	**1.704**	**1.600**
12 th	**4.062**	**3.523**	**3.648**	**-**
24 th	**4.137**	**4.514**	**2.688**	**-**
48 th	**4.172**	**4.598**	**-**	**3.900**
72 th	**4.202**	**3.583**	**-**	**-**

long as 72 hours.[110] We administered the second and third doses of Magnesium at 24 and 48 hours with an aim to maintain increased serum Magnesium concentration for a period of 72 hours. With the dosage schedule used in the present study we were successful in maintaining serum Mg levels in the neuroprotective range for a period of 72 hours.



Magnesium toxicity has been shown to relate to the serum Magnesium levels. Reportedly, symptoms of hypermagnesaemia manifest at serum Magnesium level above 5 mg/dl[111]. Babies in the study group were monitored during Magnesium infusion and every 8 hours subsequently recorded the parameters like heart rate, respiratory rate, oxygen saturation and capillary refilling time. There were no significant alterations in these parameters either with 250 mg/kg dose or with the 125 mg/kg dose, and as per our experience, these doses are safe. The maximum serum Mg level documented in the present series was 4.202 mg/dl. This can be possible reason why we did not see any side effects in the babies.

The mean number of convulsions in HIE stage 2 cases and controls were 4.61 and 7.29 respectively. There was significant reduction in number of convulsions and duration between 1st & last convulsion among the two groups. There was no significant difference in time of presentation of 1st episode of convulsion among the two groups in neonates with moderate encephalopathy. There are no major changes in analysis of convulsion or neurological outcome in patients with severe encephalopathy (HIE Stage 3).

Direct breast feeding was started on 136 hours (5 days 16 hours) and 165 hours (6 days 21 hours) of life in cases and controls respectively and the difference was significant. This finding was similar to Bhat et al and Hossain et al studies.[112]

The duration of NICU stay was 160 hours (6 days 16 hours) in cases and 195 hours (8 days 3hours) in control group. The mean duration of Oxygen supplementation was 94 hours (3 days 22 hours) and 123 hours (5 days 3 hours) in cases and controls respectively. These two variables showed a significant difference. These variables are not assessed by other studies.

One of the objectives of the present study was to monitor the complications of hypermagnesaemia in the study group. There were no significant alterations in heart rate, respiratory rate, oxygen saturation and capillary filling time were seen, following magnesium infusion with either 250 mg/kg or 125 mg/kg dose. This finding was similar to Geeta et al, Levene et al, Hossain et al and Ichiba et al studies.[113]

Neurological complications of birth asphyxia and improvement with Magnesium supplementation was studied in most of the above mentioned studies. The present study had also monitored complications of birth asphyxia in respiratory, cardiovascular, renal, hematological and gastro-intestinal system. Though the neurological outcomes were improved, there was no significant difference in the incidence of complications of birth asphyxia involving other systems were found in the present study.

SAFETY PROFILE

	Dose of Magnesium	Adverse effects
Present Study	Birth- 250mg/kg 24 hours-125mg/kg 48 hours-125mg/kg	NIL
Geeta *et al*	Birth- 250mg/kg 24 hours-125mg/kg 48 hours-125mg/kg	NIL
Bhat et al	Birth- 250mg/kg 24 hours-250mg/kg 48 hours-250mg/kg	NIL
Hossain e*t al*	Birth- 250mg/kg 24 hours-250mg/kg 48 hours-250mg/kg	NIL
Ichiba et al	Birth- 250mg/kg 24 hours-250mg/kg 48 hours-250mg/kg	NIL
Levene *at al*	Birth- 250mg/kg	NIL
	Birth- 400mg/kg	Hypotension

CONCLUSION:

1. There were 52 (61%) male babies in the total study population. In the study population, case group comprised of 45(53%) babies. Male neonates were more in both the study group.
2. 38(45%) patients had Stage 1 HIE, 35(41%) patients had Stage 2 HIE and 12(14%) patients had Stage 3 HIE. Most number of patients came in HIE stage 1 group, 20(24%) patients. Least number of patients were in HIE stage 3 control group, 5(6%) patients.
3. Mean Serum Magnesium level was lowest during birth (Case-1.795 mg/dl; Control-1.740 mg/dl). Magnesium levels were 4.062 mg/dl, 4.137 mg/dl, 4.172mg/dl, 4.202m/dlin cases during 12, 24, 48 and 72 hours of life respectively. All the serum Magnesium values in the cases were in the neuroproctective range during the 1st 72 hours of life.
4. Patients with moderate encephalopathy showed significant reduction in number of convulsions (4.6 vs 7.2) and interval between 1st & last convulsion in case group (10 vs 20 hours) in case group. There was no significant difference in time of presentation of 1st episode of convulsion among the two groups. These points out the neuroproctective effect of Magnesium supplementation.
5. Patients with severe encephalopathy showed significant reduction in time of presentation of 1st episode of convulsion among the two groups. But was no significant difference in number of convulsions and interval between 1st & last convulsion among the two groups.

6. Case group showed significant reduction duration of oxygen supplementation (94 vs 123 hours), time initiation of DBF (136 vs 165 hours of life) and duration of NICU stay (160 vs 195 hours) as compared to controls.
7. Complications of birth asphyxia (other than neurological system) were similar in both the groups.

SUMMARY

The present study was done as a randomized study involving 85 term neonates (45 cases and 40controls) with birth asphyxia in which the cases were supplemented with Magnesium and the complications and outcome were compared with the control group.

Significant differences in Magnesium level were seen in cases after supplementation. Case group with moderate encephalopathy showed significant reduction in number of convulsions and interval between 1st & last convulsion among the two groups. There was significant reduction in case group on duration of oxygen supplementation, initiation of DBF and duration of NICU stay.

Decrease in the number of convulsion and duration of convulsion shows the neuroprotective effect of Magnesium in treatment of birth asphyxia. In the present study Magnesium supplementation regimen was not associated with toxicity. There was no difference in complications (other than neurological system).

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ANNEXURE

ETHICAL CLERANCE CERTIFICATE

PROFORMA

SCHEME OF CASE TAKING :

NAME : CASE / CONTROL

SEX : IP NO :

RELIGION : DOA :

POSTAL ADDRESS: DOD :

APGAR SCORE

MATERNAL MEDICAL HISTORY -:

INTRAPARTUM HISTORY:

GENERAL PHYSICAL EXAMINATION:

EGA : by dates …… weeks : by exam …… weeks ;

LENGTH ……..cms ; HC ……cms

BIRTH WEIGHT ……. gms . MAC ……. Cms

SYSTEMIC EXAMINATION

- Cardiovascular System

- Respiratory System

- Gastro-intestinal system

- Central Nervous System

ROUTINE INVESTIGATION RESULT:

MAGNESIUM ESTIMATION RESULT:

COMPLICATIONS AND OUTCOME:

CONSENT FORM

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT:

STUDY ON SHORT-TERM OUTCOME OF BIRTH ASPHYXIA TREATED WITH MAGNESIUM

GUIDE :

CO-GUIDE :

P G STUDENT :

PURPOSE OF RESEARCH:

I have been informed that the present study will help in assessing the outcome and complications in birth asphyxia and improve the quality of life in neonates

PROCEDURE:

I understand that after having obtained a detailed clinical history, thorough clinical examination and relevant investigations, the child will receive Magnesium sulfate infusion at 250 mg/kg per dose (in 20 mL of 5% dextrose solution) over 1 hour within first hour of birth, and 2 additional doses 125 mg/kg per dose (in 20 mL of 5% dextrose solution) over 1 hour at intervals of 24 hours.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomforts during the examination or during my treatment. This is mainly the result of my condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in the study will have no direct benefit to me other than the potential benefit of the treatment.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of

sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time; Dr.Sajith.J.S at the department of pediatrics is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Sajith.J.S may terminate my participation in the study after he has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me. But, no further compensation would be provided

by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that Dr.Sajith.J.S is doing a study on SHORT-TERM OUTCOME OF BIRTH ASPHYXIA TREATED WITH MAGNESIUM. has explained to us the purpose of research and the study procedure. We are willing to allow our baby to undergo the treatment with magnesium, investigations and the possible discomforts as well as benefits. We have been explained all the above in detail in our own language and we understand the same. Therefore we agree to give consent to participate as a subject in this research project.

_____ _____

(Parents / Guardian) Date

_____ _____

(Witness to signature) Date

KEY TO MASTER CHART

S.Mg	Serum Magnesium
DBF	Direct Breast feeding
B/o	Baby of
HIE	Hypoxic Ischemic Encephalopathy
GMH	Germinal Matrix Hemorrhage
IVH	Intra Ventricular Hemorrhage
PAH	Pulmonary Artery Hemorrhage
FI	Feed intolerance
HYB	Hyperbilirubinemia

MASTER CHART

Sl No.	Name	IP No	Study group	sex	S.Mg level(Hours of life)					Starting of DBF (Hours)	Duration of Oxygen Dependence(Hours)	HIE Stage	Episode of 1st Conulsion (Hours)	Number of Convulsion	Interval between convulsion (Hours)	Duration of NICU Stay (Days)	Complication
					0	12	24	48	72								
1	B/o Savita	26943	Case	Female	2.11	4.18	4.01	4.33	4.33	96	72	1	0	0	0	4	-
2	B/o Sunanda	12736	Control	Female	1.61	1.68	1.73	1.66	1.72	192	144	1	0	0	0	9	-
3	B/o Renuka	12960	Control	Female	2.16	2.11	2.01	1.96	2.13	156	108	1	0	0	0	8	-
4	B/o Lakshmi	6480	Case	Female	1.67	3.21	3.89	4.12	4.19	108	48	1	0	0	0	6	-
5	B/o Shruti	6509	Case	Female	1.83	4.31	4.11	4.16	4.11	223	108	1	0	0	0	6	-
6	B/o Sharanamma	30735	Case	Female	1.65	3.88	3.91	3.86	4.36	132	72	1	0	0	0	6	-
7	B/o Yashodha	13/69	Case	Female	1.87	3.96	4.24	4.18	4.18	216	192	1	0	0	0	9	PAH
8	B/o Savitri	13801	Control	Female	1.46	1.61	1.63	1.66	1.58	132	120	1	0	0	0	7	-
9	B/o Pushpa	30291	Control	Male	1.48	1.58	1.65	1.64	1.59	228	216	2	2	10	15	1	-
10	B/o Sumitra	28253	Case	Female	1.54	4.78	3.91	3.84	3.82	96	36	1	0	0	0	6	-
11	B/o Kavita	30458	Case	Female	2.11	3.96	3.88	3.94	4.31	132	56	1	0	0	0	8	FI
12	B/o Saraswati	30316	Control	Male	1.48	1.66	1.76	1.73	1.81	192	166	2	10	10	16	9	FI
13	B/o Roopa	18674	Control	Female	2.22	2.11	2.18	2.01	2.31	166	108	1	0	0	0	8	-
14	B/o Sarojini	22381	Control	Female	2.11	2.35	2.41	2.51	2.36	144	120	1	0	0	0	8	-
15	B/o Mahadevi	21908	Control	Female	1.36	1.45	1.44	1.39	2.31	159	109	1	0	0	0	2	GMH
16	B/o Sangamma	13/194	Case	Female	1.88	4.15	4.19	4.30	4.13	144	128	1	0	0	0	7	-
17	B/o Annapurna	13/676	Case	Female	2.36	4.61	4.22	4.38	4.39	156	72	1	0	0	0	7	FI
18	B/o Shilpa	1778	Case	Female	2.01	4.18	4.15	4.31	3.84	144	56	1	0	0	0	7	HYB
19	B/o Saraswati	30315	Control	Male	1.66	1.68	1.74	1.81	1.7	240	240	2	2	9	14	14	IVH
20	B/o Rekha	3302	Case	Female	1.43	3.67	3.56	3.79	4.31	132	108	1	0	0	0	6	-
21	B/o Sangeeta	4901	Case	Female	1.75	3.92	4.19	4.18	4.19	132	120	1	0	0	0	7	GMH
22	B/o Gayatri	5081	Case	Female	1.61	3.69	4.85	4.16	4.16	144	102	1	0	0	0	7	-
23	B/o Malanbee	6364	Control	Male	2.21	2.16	2.31	2.03	1.98	204	168	3	4	2	33	13	PAH
24	B/o Renuka	7946	Control	Male	2.13	2.11	2.01	1.92	2.19	0	96	3	4	4	32	4	Death
25	B/o Sujatha	10120	Case	Male	1.94	4.22	4.75	4.54	4.12	132	120	2	1	8	16	6	-

26	B/o Sarita	10213	Case	Male	2.23	4.18	4.22	4.41	4.25	120	108	2	1	9	20	6	-
27	B/o Rekha	11339	Case	Male	1.99	4.03	3.96	3.91	4.36	144	72	2	1	5	15	7	HYB
28	B/o Shridevi	28284	Control	Male	1.83	1.91	1.88	1.75	1.84	144	120	1	0	0	0	7	-
29	B/o Deepa	18897	Control	Female	1.66	1.73	1.68	1.88	1.63	136	120	1	0	0	0	3	-
30	B/o Nagamma	11543	Case	Male	1.66	3.88	4.46	4.11	4.38	120	102	2	1	6	8	6	-
31	B/o Sabawwa	1672	Control	Male	1.56	1.71	1.63	1.78	1.79	0	88	2	9	9	22	4	Death
32	B/o Ambika	11599	Case	Male	2.29	4.16	4.69	4.31	4.85	120	62	2	1	4	3	7	FI
33	B/o Priyanka	10553	Case	Male	2.17	4.34	4.13	4.22	3.94	192	168	2	1	4	3	9	IVH
34	B/o Shivaleela	28094	Case	Female	1.38	4.53	3.66	4.33	3.78	98	56	1	0	0	0	3	-
35	B/o Siddanna	27317	Control	Female	1.88	1.94	1.91	1.71	1.76	144	102	1	0	0	0	7	-
36	B/o Laxmi	28248	Control	Female	1.48	1.46	1.58	1.66	1.76	168	148	1	0	0	0	9	GMH
37	B/o Pavitra	14471	Case	Male	1.89	4.14	4.61	4.66	4.33	168	144	2	1	10	12	8	PAH
38	B/o Rekha	14598	Case	Male	1.99	4.35	4.11	4.26	4.19	144	108	3	2	7	24	8	-
39	B/o Manjula	14599	Case	Male	1.77	4.43	3.86	3.88	3.95	144	120	3	1	6	22	8	IVH
40	B/o Shruti	14902	Case	Male	1.68	3.91	3.76	3.73	4.26	120	96	3	2	8	38	6	-
41	B/o Rekha	12039	Case	Male	1.48	3.71	4.38	4.41	4.36	108	72	3	1	8	24	6	-
42	B/o Mahadevi	12243	Case	Male	1.94	4.55	4.34	4.16	4.26	0	80	3	5	3	8	4	Death
43	B/o Jayashri	12386	Case	Male	1.79	3.94	4.37	4.41	4.06	0	120	3	2	3	20	5	Death
44	B/o Gayatri	21135	Control	Female	2.07	2.39	2.2	2.35	2.07	108	72	1	0	0	0	6	-
45	B/o Swapna	22858	Control	Female	1.54	1.66	1.65	1.46	1.59	216	128	1	0	0	0	16	GMH
46	B/o Bharati	27037	Control	Female	2.16	2.27	2.21	1.95	1.9	144	78	1	0	0	0	8	-
47	B/o Afrana	7988	Case	Male	1.44	3.66	3.73	3.88	4.23	156	128	2	1	2	6	8	GMH
48	B/o Sudha	18880	Control	Female	1.28	1.36	1.44	1.39	1.66	216	192	1	0	0	0	12	RF
49	B/o Jyothi	29992	Control	Male	1.36	1.46	1.58	1.75	1.84	185	142	2	1	9	25	1	-
50	B/o Savitha	3020	Case	Female	1.46	4.74	3.88	3.91	4.16	144	128	1	0	0	0	7	RF
51	B/o Kavitha	13883	Control	Female	1.49	1.66	1.58	1.69	1.63	144	120	1	0	0	0	7	-
52	B/o Renuka	20408	Control	Female	1.79	1.86	1.88	1.76	1.87	132	108	1	0	0	0	6	PAH
53	B/o Shyadbee	8111	Case	Male	1.83	4.01	4.63	4.05	4.14	120	108	2	6	1	0	7	PAH
54	B/o Akarshika	8704	Case	Male	1.43	3.75	3.8	3.75	3.89	120	84	2	3	2	14	6	
55	B/o Savitri	29114	Control	Male	1.81	1.91	1.83	1.8	1.80	144	84	1	0	0	0	7	FI
56	B/o Gurabai	6682	Case	Male	1.48	3.88	3.86	4.14	4.36	156	108	1	0	0	0	7	GMH
57	B/o Shantabai	7096	Case	Male	1.85	4.16	4.64	4.88	4.28	108	90	1	0	0	0	6	-
58	B/o Jayawwa	19467	Control	Female	1.94	1.86	1.88	1.91	1.89	120	108	1	0	0	0	6	-
59	B/o Bhuvana	2150	Control	Male	1.75	1.84	1.74	1.81	1.88	166	108	2	1	8	28	8	HYB
60	B/o Savita	3020	Control	Male	1.85	1.96	1.78	1.94	1.16	120	48	2	3	10	12	7	-
61	B/o Channawwa	3900	Control	Male	2.26	1.81	1.75	2.14	1.89	192	156	2	4	4	13	9	PAH
62	B/o Remya	12421	Case	Female	1.81	4.01	4.34	4.55	4.36	143	108	3	3	2	24	8	-
63	B/o Rekha	27946	Case	Female	1.81	4.16	4.12	4.24	4.09	120	72	1	0	0	0	6	-
64	B/o Basamma	8125	Control	Male	1.56	1.44	1.59	1.71	1.73	144	87	3	5	5	30	7	-

65	B/o V\idyarani	6628	Case	Male	1.69	3.95	3.95	4.13	4.23	108	72	1	0	0	0	6	-
66	B/o Vaishali	2894	Control	Male	1.56	1.81	1.63	1.81	1.89	120	89	2	2	7	26	7	-
67	B/o Kavita	1704	Control	Male	1.59	1.41	1.49	1.68	1.73	144	66	2	2	6	16	7	FI
68	B/o Jayashri	1953	Control	Male	1.45	1.63	1.66	1.53	1.61	228	216	2	2	4	26	14	PAH
69	B/o Anita	7443	Case	Male	1.69	3.88	3.93	4.54	4.09	120	108	1	0	0	0	7	HYB
70	B/o Laxmibai	7881	Case	Male	1.73	3.94	4.39	4.14	3.61	84	66	2	5	1	0	5	-
71	B/o Shankrawwa	4219	Control	Male	2.05	2.16	2.11	2.31	2.35	168	96	2	9	1	0	8	HYB
72	B/o Hema	5649	Control	Male	1.55	1.52	1.65	1.69	1.81	108	98	2	1	8	20	11	IVH
73	B/o Bourawwa	6178	Control	Male	1.39	1.48	1.65	1.61	1.58	216	120	2	1	6	26	13	-
74	B/o Mahananda	9196	Case	Male	1.69	3.71	3.68	3.88	4.31	108	36	2	1	2	12	6	-
75	B/o Arati	9726	Case	Male	1.59	3.94	4.09	4.01	4.31	216	24	2	1	5	8	10	RF
76	B/o Nagamma	10011	Case	Male	1.93	3.84	4.56	4.92	4.16	0	120	2	3	2	10	5	Death
77	B/o Laxmi	9910	Case	Male	1.81	4.51	4.03	4.33	4.71	120	72	2	2	6	9	6	-
78	B/o Nasreen	5437	Control	Male	1.79	1.88	1.86	2.12	2.32	192	168	2	2	11	10	9	-
79	B/o Asparabanu	1587	Control	Male	1.78	1.94	1.86	1.94	1.81	0	72	2	1	6	30	3	Death
80	B/o Vaishali	3414	Control	Male	1.46	1.52	1.62	1.54	1.74	192	144	2	3	6	33	8	-
81	B/o Neelamma	11151	Case	Male	1.86	3.96	3.96	3.14	4.05	144	90	2	6	1	0	7	-
82	B/o Shobha	14118	Case	Male	1.66	3.83	4.14	4.19	4.36	132	120	2	6	3	8	8	GMH
83	B/o Afrin	14311	Case	Male	1.88	3.99	4.03	4.18	4.32	108	96	2	2	12	6	7	
84	B/o Parvati	7678	Control	Male	2.16	2.19	2.01	2.16	2.31	240	168	3	5	2	38	12	IVH
85	B/o Bhanubai	8144	Control	Male	1.68	1.75	1.66	1.79	1.76	0	88	3	5	4	20	4	Death