STUDY ON

"EEG AT ONE MONTH OF AGE OF NEW BORN BABIES WHO UNDERWENT THERAPEUTIC HYPOTHERMIA USING LOW COST TECHNOLOGY IN A LEVEL 2 NICU SETTING – A PROFILE"

Dissertation Submitted in partial fulfillment of

M.D. DEGREE EXAMINATION

M.D. PAEDIATRICS—BRANCH VII

CHENGALPATTU MEDICAL COLLEGE, CHENGALPATTU.

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
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CERTIFICATE

This is to certify that this dissertation titled -**"EEG AT ONE MONTH OF AGE OF NEW BORN BABIES WHO UNDERWENT THERAPEUTIC HYPOTHERMIA USING LOW COST TECHNOLOGY IN A LEVEL 2 NICU SETTING – A PROFILE".** has been prepared by Dr.V.NAGARAJAN, under my supervision in the Department of Paediatrics, Chengalpattu Medical College, Chengalpattu during the academic period 2010-2013 and is being submitted to the Tamil Nadu DR.M.G.R. Medical University, Chennai in partial fulfillment of the University regulation for the award of the M.D., Branch - VII, (Pediatrics) and his dissertation is a bonafide work.

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DECLARATION

I **Dr.V.NAGARAJAN**, solemnly declare that this dissertation **"EEG AT ONE MONTH OF AGE OF NEW BORN BABIES WHO UNDERWENT THERAPEUTIC HYPOTHERMIA USING LOW COST TECHNOLOGY IN A LEVEL 2 NICU SETTING –A PROFILE"**

is a bonafide record of work done by me in the Department of Paediatrics, Govt. Chengalpattu Medical College and Hospital,Chengalpattu, under the guidance of Prof.Dr.M.UMAKANTHAN. M.D.Department of Paediatrics, Govt. Chengalpattu Medical College and Hospital, Chengalpattu.

This dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the University regulations for the award of M.D. Branch - VII, (Pediatrics) Examination to be held in April 2013.

Place : Chengalpattu

Date : 25.12.2012

Dr V.NAGARAJAN

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2) Letter dated 27.03.2012 of the Head of the Department of Paediatrics, Chengalpattu Medical College, Chengalpattu.

...

Dr.V.Nagarajan, Post Graduate Student in M.D.(Paediatrics) of this college has submitted a Dissertation for the study work entitled "EEG at one month of age of New Born Babies who underwent therapeutic hypothermia using low cost technology in a level 2 NICU setting – a profile". The study of the above Dissertation Work of the above Individual has been approved by the Human Ethical Committee of the Chengalpattu Medical College, Chengalpattu which is forwarded herewith for further course of action.

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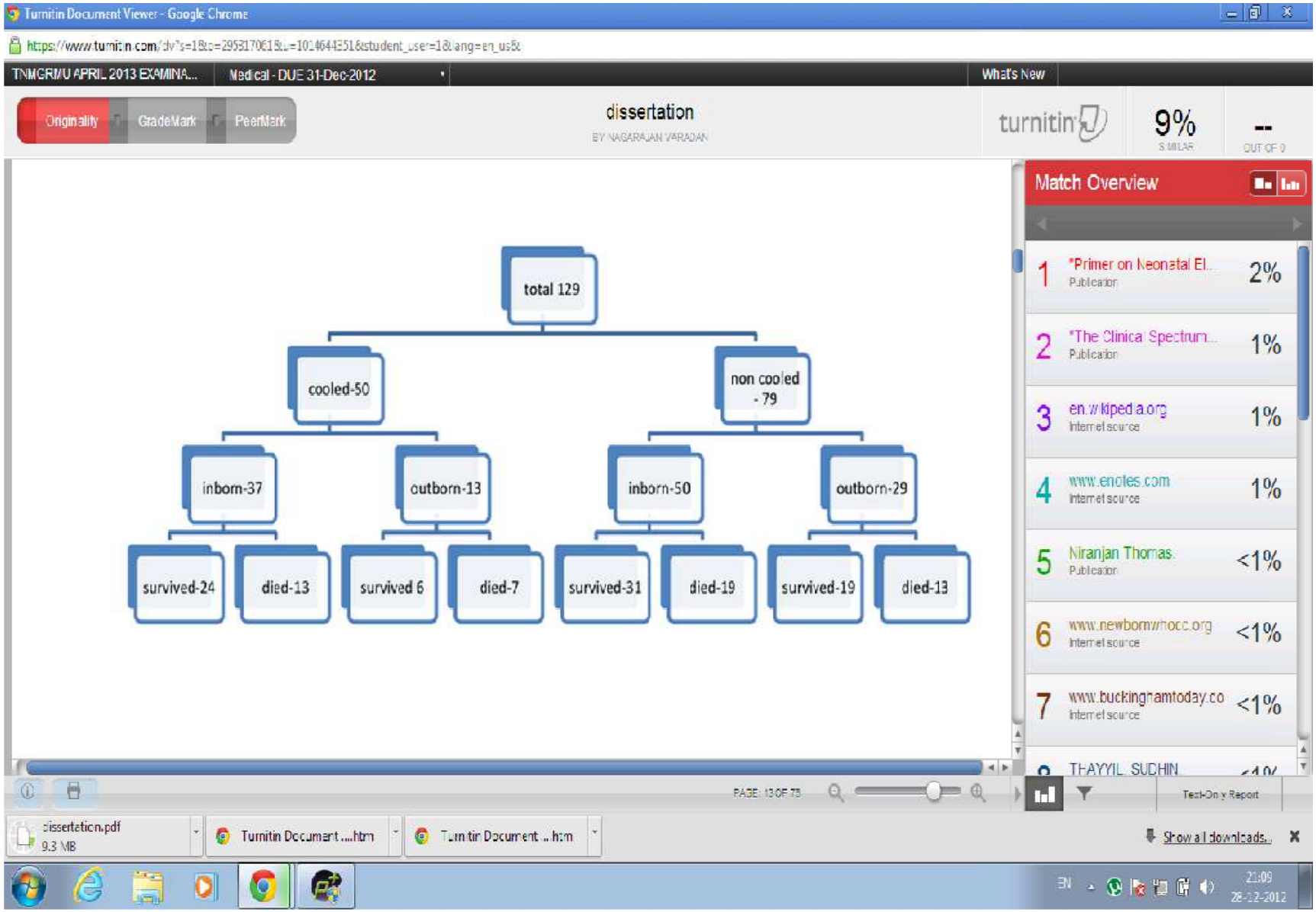
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INTRODUCTION

EPIDEMIOLOGY:

Perinatal hypoxia is one of the leading contributor to both neonatal mortality and neurodevelopmental disability. The reported incidence of perinatal hypoxia in developed countries is around 1-1.5%.

The incidence of perinatal hypoxia reported in India is higher ie., around 2.5% according to NNPD 2000 data.

Perinatal hypoxia contributes to major share of neonatal deaths in India – nearly 20% of neonatal mortality. If still births were included the contribution from perinatal hypoxia will increase further.

THERAPEUTIC HYPOTHERMIA:

Until recently recently there is no specific treatment for perinatal hypoxia. Treatment basically involves supporting the organ systems. There were immense clinical research in various neuroprotective strategies in perinatal hypoxia.

Among these therapeutic hypothermia holds promise. Within a short span of time therapeutic hypothermia become a standard of care and in many western countries registry maintained nationwide for this new procedure.

Indeed therapeutic hypothermia was mentioned in neonatal resuscitation protocol by American academy of paediatrics.

Feasibility trial done in CMC vellore acknowledge to the fact that this procedure could be adapted to a low cost setting in a safe manner .

In this method newborns suffering from moderate to severe encephalopathy would be intentionally subjected to a controlled hypothermia for 72 hrs.

Follow up studies(TOBY TRIAL) at 18 months showed better neurodevelopmental outcome. Assessment of neurodevelopment at school age(TOBY TRIAL FOR CHILDREN) is still on the way.

If this technology could be adapted to a low cost form it would benefit a great number of newborns in developing countries like India.

EEG is an valuable investigation in that it can assess the function of the brain unlike other imaging studies. EEG is used in perinatal hypoxia to grade the severity, to prognostic the developmental outcomes, to identify seizures .

In this study I analysed the EEG records of those babies who underwent therapeutic hypothermia as a treatment for hypoxic ischemic encephalopathy from the month of May 2012 to november 2012 in Chengalpattu medical college neonatal intensive care unit – a level II nicu setting and the statistics were presented.

INTRODUCTION TO THERAPEUTIC HYPOTHERMIA:

HISTORY:

The concept of using cooling the body as a treatment strategy was an age old one. It was even during age old period Hippocrates – Father of Medicine advised regarding the use of ice to reduce the swelling among wounded soldiers.

One of the surgeons of the great warrior Napoleon made an interesting observation during the periods of war. According the soldiers of higher cadre who were sheltered near the fire tend to die more frequently than the ordinary low grade soldiers who were left in the cold to suffer.

THERAPEUTIC HYPOTHERMIA IN ADULTS:

One of the first article regarding therapeutic hypothermia appeared in 1945. Then scientific people lost interest in it. Animal experiments involving therapeutic hypothermia was conducted in 1984.

The Skiing accident of Anna Begholm who was resuscitated after a long period of cardiac arrest from the ice cold water arose interest among scientist about the neuroprotective possibility of hypothermia in cardiac arrest situations.

Nowadays therapeutic hypothermia is a recognized treatment option for cardiac arrest patients in adults. In 2002 the American heart association and ILCOR – international liason and committee on resuscitation endorsed the procedure of therapeutic hypothermia for cardiac arrest patients.

Inducing therapeutic hypothermia in adults is limited to few centers in developed countries. Therapeutic hypothermia is also tried in few other clinical scenarios- head injury, traumatic spinal cord injury, stroke, neurogenic fever.

THERAPEUTIC HYPOTHERMIA IN NEONATES:

The scenario of therapeutic hypothermia for perinatal asphyxia is somewhat different. Initially few scientist were involved in animal experiments for the effect of hypothermia in thyroid function.

The experiments evolved to analyzing the hypothermia effects in asphyxiated animals in piglets and sheep by using complex gadgets like magnets resonance spectroscopy analysis and also simple instruments like EEG.

The first pilot study on the effect of therapeutic hypothermia was conducted in human babies in New Zealand in 1998 and prove to the point that the procedure was safe and it is really a feasible option.

THERAPEUTIC HYPOTHERMIA CLINICAL TRIALS:

Suddenly interest in the concept of neuroprotective effect of therapeutic hypothermia spread to many countries. Subsequent pilot studies were conducted in Australia, US, Turkey, China.Three major multicentered randomized clinical trials –COOL CAP STUDY, NICHD STUDY, TOBY STUDY about the period of 2003-2005 in countries such as US,UK, New Zealand and Australia.

THERAPEUTIC HYPOTHERMIA TRIAL RESULTS:

In 2007 Cochrane group analysed the metaanalysis of the report particularly that of TOBY trial and concluded that although therapeutic hypothermia does not reduce the mortality and severe neurodevelopmental sequale therapeutic hypothermia is associated with a better neurodevelopmental outcomes.

ENDORSEMENT OF THERAPEUTIC HYPOTHERMIA:

Subsequently many hospitals particularly those countries and centers involved in the trials were started offering therapeutic hypothermia as a treatment option for perinatal asphyxiated neonates.

In many of this developed countries national registry exists for providing uniformity in the treatment of therapeutic hypothermia in various hospitals. The number of hospitals providing therapeutic hypothermia constantly growing since then.

In developed countries therapeutic hypothermia is induced by a servo control machine than regulates the temperature of the water in the blanket. The baby will be kept over the blanket.

In US there is a tendency to monitor the core temperature of the baby during the cooling procedure by oesophageal thermometer as it more closer to brain.

Instead in UK rectal probe was used to measure the core temperature. Therapeutic hypothermia is endorsed by NICE –UK and also recommended in neonatal resuscitation protocols by American academy of paediatrics.

THERAPEUTIC HYPOTHERMIA USING LOW COST TECHNOLOGY:

The high prevalence of perinatal asphyxia and its attended high mortality and high morbidity in developing countries arouse serious interest in this new technology.

Anectodally developing countries like India, South Africa, China were conducting clinical trials in therapeutic hypothermia for perinatal asphyxiated newborns.

THERAPEUTIC HYPOTHERMIA IN INDIA:

In India study conducted by Dr.Niranjan Thomas of CMC vellore proved to the point that therapeutic hypothermia can be induced by a low cost technology such as gel packs and vaccine carriers in an effective and safe manner.

Indeed even in those centers were therapeutic hypothermia is induced by servo control machine babies were used to cooled by gel packs while during the inter hospital transport. So the concept of inducing therapeutic hypothermia by gel packs is not entirely new one.

The average cost of servo control machine involved in therapeutic hypothermia would be around 35 lakhs interms of Indian money. Comparatively inducing hypothermia by gel packs is relatively much cheaper and feasible option which also doen't need expertise management.

There are interests in Phase contrast materials which tend to retain the temperature relatively stable than the gel packs.

Various ingineous low cost technology in inducing hypothermia was tried. For example in one of the African countries water bottles was used to induce hypothermia and in one another study electrical fan was used.

Ìn India CMC Vellore and Jipmer Pondicherry were pionnerring in this field of therapeutic hypothermia. Jipmer have produced several molecular studies proving the neuroprotective efficacy of therapeutic hypothermia in perinatal asphyxia.

National wide conferences and indeed workshops are being conducted in India regarding this new technology of therapeutic hypothermia.

AIM OF THE STUDY:

To analyse the EEG pattern of neonates who suffered hypoxic ischemic encephalopathy and underwent therapeutic hypothermia as a treatment modality.

OBJECTIVE OF THE STUDY

1.To identify subclinical seizures and follow them with developmental assessment, clinical neurological examinations, anthropometric measurements.

2. To identify abnormalities in EEG associated with clinically suspected seizures and thereby treating with anticonvulsants.

3. To identify abnormalities in EEG associated with developmental delay concerns.

4.To have a baseline EEG record so that follow up serial EEG assessment can be made to prognosticate neurodevelopmental outcome in perinatal hypoxia.

5.To identify any EEG abnormalities associated with structural abnormalities.

MATERIALS AND METHODS:

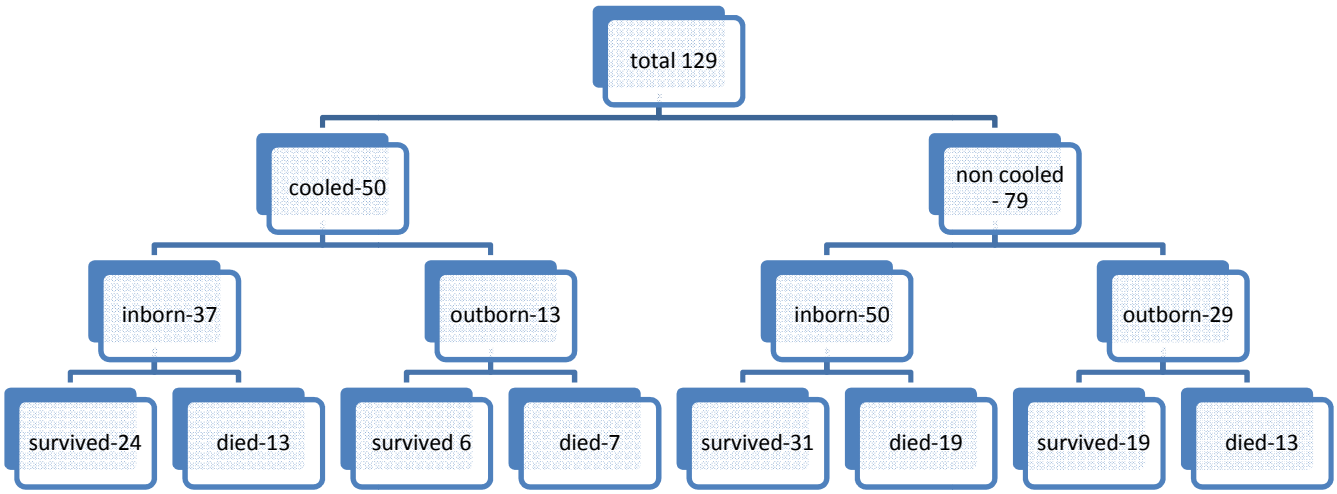
Those babies who underwent therapeutic hypothermia as a treatment for moderate to severe encephalopathy would be qualified to undergo EEG testing at the age of one month.

In our institution from the month of May 2012 to November 2012 about 129 term newborns were admitted for moderate to severe hypoxic ischemic encephalopathy.

Of these 129 newborns 42 babies were delivered in institutions other than Chengalpattu Medical College Hospital and reffered here. Remaining 87 were delivered in our institution.

Out of the total 129 babies about 50 babies underwent therapeutic hypothermia after getting informed consent and satisfying the inclusion criteria.

There is no random allocation between cooled and non cooling groups. Every babies satisfying the inclusion criteria will be offered therapeutic hypothermia as a treatment option.


total 129
cooled-50
non cooled - 79
inborn-37
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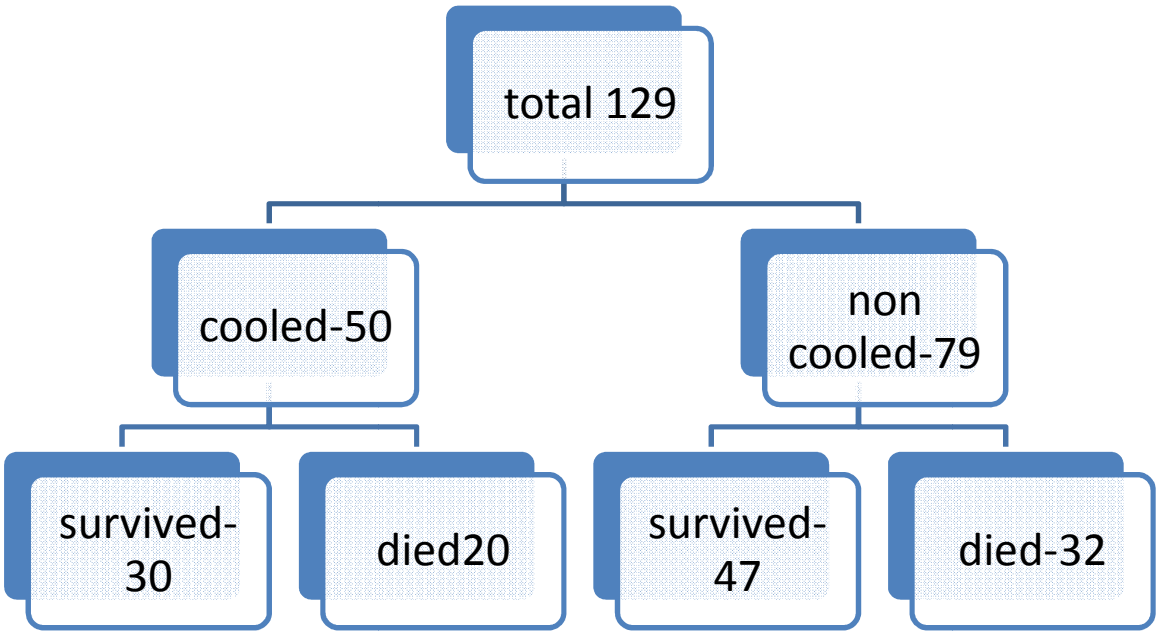


INCLUSION CRITERIA:

1. Term(>36wks)
2. Birthweight > or equal to 2000g
3. Apgar score of less than or equal to 5 at the age of 10 mins of life
4. less than 6 hrs of life
5. features of moderate to severe encephalopathy as classified by levene staging of hypoxic ischemic encephalopathy.
6. Prolonged need for ventilator assistance – either by bag and mask ventilation or Endotracheal intubation even after 10 minutes of life.

EXCLUSION CRITERIA:

1. Refusal of consent
2. >6 hrs of life on admission or features of encephalopathy diagnosed at >6 hrs of life
3. major congenital anomalies
4. inability to intiate cooling by 6 hrs of age

After satisfying the inclusion and exclusion criteria those babies selected for therapeutic hypothermia will be started on cooling as quickly as possible. Cooling was done by gel packs and vaccine carries.

Gel packs and vaccine carriers would be kept in refrigerator before use.Gel packs and vaccine carriers will covered with clean cloth and kept around the baby which has to be cooled.

A rectal probe PHILIPS –ref no 21090A was used to constantly monitor the rectal temperature. The probe will be inserted about 5 cm into the rectum from the anal margin All the vital parameters will be monitored continuously.

The gel packs and vaccine carriers would be constantly removed and replaced around the baby so that the core temperature would be around 33-34 celcius with an acceptable range of 32.5 to 34.5 celcius.

This particular target temperature 33-34 degree celcius will be maintained for the next 3 days or 72 hrs. Babies will be constantly repositioned to avoid subcutaneous fat necrosis.

Bladder will be cathetrised to monitor urine output. Prothrombin time and activate partial thromboplastin time will be assessed for coagulopathy. If coagulopathy is found fresh frozen plasma will be transfused and the investigation would be repeated.

Other blood investigation would be done as per the standard management of perinatal hypoxia.Monitoring during the cooling and rewarming period will be documented in the specially modified monitoring charts.

At the end of 72 hrs babies would be gradually rewarmed over a period of 10 hrs with the temperature increasing not more than 0.5 celcius per hour to avoid rebound hyperthermia.

Data regarding the babies who underwent the therapeutic hypothermia would be collected and analysed systematically. The residential address and phone numbers of the parents will be collected.

The date for EEG examination of the baby will be fixed just before the baby gets discharged and the parents will be informed both orally and written forms regarding the date of EEG examination.

Occasionally babies may require sedation during the procedure of recording EEG . In that case Chloral hydrate – which will not affect the EEG patterns was used.

Every baby would undergo imaging in the form of ultrasound cranium before getting discharged. Parents will be given follow up book made for nicu graduates of our institution.

EEG will be recorded in the EEG unit of Neurology Department of our Institution and the data will be maintained. EEG will be analysed by Neurologist and the results are communicated to the parents and the need for regular follow up visit is also instructed.

Developmental screening of the babies who underwent therapeutic hypothermia was planned. Developmental screening was done by using DDST II Denver Developmental Screening Test by me.

DDST screening for all these babies were done in the month of December 2012 in two session with the average time taken for each babies was 10 minutes. So babies of various age groups – from one month age to 7 months were tested by DDST.

Parents were called to attend the screening test by phone. The nature of the screening test and the results of the test were instructed to the parents.

During this developmental assessment follow up, head circumference and the weight of the baby was also measured. Weight of the babies were measured using taring scales.z scores of the head circumference and weight of the baby will be derived from the free software ANTHRO provided by WHO official website.

REVIEW OF LITERATURE:

PERINATAL HYPOXIA:

Neonatal mortality is high in India as in many developing countries. The neonatal mortality is about 36/1000 live births in India-and about 23/1000 live births in the state of Tamil Nadu- Sample registration System-Statistical Report 2007 Ministry of Home Affairs New Delhi.

Neonatal mortality rate in India – 32/1000 live births – WHO REPORT 2010. Total number of neonatal deaths in India during the year 2010 – 8,75,000.

Data regarding the contribution of perinatal hypoxia to the neonatal deaths were obtained from hospitalized babies.

Among intramural babies perinatal asphyxia contributes more than 50% of mortality and among extramural babies perinatal asphyxia contributes to nearly 49% of neonatal moratlity.- National Neonatal and Perinatal Database NNPD 2002-2003.

Thus in India perinatal hypoxia is a leading cause of neonatal mortality. It is assumed that perinatal mortality contributes to nearly 20% of neonatal mortality overall in India,

According to NNPD 2000 data about 2.5% babies continued to have Apgar score of less than 7 at 5 minutes of age. Thus the prevalence of perinatal hypoxia and its consequences are relatively high in India compared to developed countries.

Among the survivors of perinatal asphyxia 5-10% may develop cerebral palsy compared to the risk of only 0.2% in the general population.

THERAPEUTIC HYPOTHERMIA:

HISTORY:

Hypothermia as a treatment modality is not new to mankind. It was even during age old time that Hippocrate advised to use ice packs for wounded soldiers.

An interesting observation by one the Naploean's surgeon Dominique Jean larrey was that officers who sheltered near fire survived less often than lower grade soldiers during the period of war.

The first medical article regarding use of hypothermia in the treatment appeared in 1945 in which hypothermia was used in head injury patients.

Doctor Rosomoff demonstrated the neuroprotective beneficial effects of hypothermia in dogs in 1950s.

Skiing accident of Anna Bagenholm in 1999 is an important milestone in therapeutic hypothermia.

Besides animal studies and human accidents the first human experiments regarding therapeutic hypothermia appeared in 2002.-Holzer, Michael-“ Mild hypothermia to improve the neurologic outcome after cardiac arrest”New England Journal of Medicine. 2002 vol.346 no.8

In 2003 American Heart Association and International Liason Committee on resuscitation endorsed the application of therapeutic hypothermia as a treatment modality for cardiac arrest candidates in adults.

Along with this various experiments involving neuroprotective role of various drugs were suggested as a treatment modality for therapeutic hypothermia.

Vannuci RC, Current and potentially new management strategies for perinatal hypoxia ischemic encephalopathy. Paediatrics 1990;85:961-8

Du-Pleiss and Johston explored the cellular mechanism and potential strategies for neuroprotection- Clinics in perinatology 1997:29.627-654

In one of the trials high dose phenobarbitone was tried as a neuroprotective statergy- Hall RT, Hall FK, Daily DK - J Paediatr 1998;345-8

Agents such as ketamine,MK-80, allopurinol, superoxide dismutase and vitamin E; Ca channel blockers – nimodipine,nicardipine; cyclooxygenase inhibitor such as indomethacin; benzodiazepine receptor stimulation such as midazolam; and protein synthesis enhancers such as dexamethosone have been tried in animal experiments as a neuroprotective strategy in perinatal hypoxia. These experiments have few or no human experimental data.

Xenon and Erythropoietin are promising agents in this front and they are in Phase I clinical trial and in one major trial is conducted along with therapeutic hypothermia for its possible synergestic benefit.Xe-hypotheca trial-Turku university hospital.

TOBY one of the major clinical trials involved in therapeutic hypothermia in perinatal asphyxia is now conducting trial (TOBY Xenon -2009-2012) in the beneficial neuroprotective effects of Xenon.

THERAPEUTIC HYPOTHERMIA IN NEONATES – EVOLUTION:

1.Gluckman and Gunn – endocrinologist – University of Auckland New Zealand – interested in cooling for its effect on thyroid function.

2.Reynold group conducted hypothermia experiments in newborn piglets-1994 “Delayed (secondary) cerebral energy metabolism and infaction following acute hypoxia-ischaemia in the newborn piglet continous 48 hour studies by 31P magnetic resonance spectroscopy” Paediatr Res 36(6) 699-706

3.Alistair gunn and Chris Williams conducted hypothermia experiments in fetal sheep-1992 “Outcome after ischemia in the developing sheep brain: an electroencephalographic and histological study”Ann Neurol 31(1):14-21

4.1998- The first pilot randomized control trial of therapeutic hypothermia was conducted in Newzealand. It included 31 newborn infants with HIE. This milestone experiment was demonstration of the proof of principal, feasibility in humans. This experiment arouse intense curiosity and was followed by 4 other pilot trials from U.S, Australia, Turkey and China.

5. 2005 Three separate multicenter randomized control trials – conducted in US,UK,Australia, New Zealand

a.) The Cool Cap Study – the first infant was enrolled on july 1999 ; full publication in The Lancet in 2005 – no significant beneficit in reducing death or disability at 18 months but benefit was shown when infants with severe or long established neuronal damage was excluded from the study.

b.) The National Institute of Child Health and Human Development Study led by Seetha Shankaran – NICHD trial found a significant benefit. The study was critised for temperature instability in the control group.

c.) TOBY Trial –Total Body hypothermia for perinatal asphyxia trial led by Azzopardi- six year study from September 2002- August 2008.

Recruitment to TOBY ended on 30th November 2006 and its 18 month Follow up was completed in autumn 2008. The results of the trial was published in New England Journal of Medicine in October 1,2009;361:1349-1358

The clinical trial arrived at a final conclusion that moderate hypothermia for 72 hours in infants who had perinatal asphyxia did not significantly reduce the combined rate of death or severe disability but resulted in improved neurologic outcomes in survivors.-BIO MED CENTRAL BMC Paediatrics 2008,8:17 doi:10.1186/1471-2431-8-17

The number needed to treat of 8 for intact survival and 14 for mortality is remarkable for any medical theraphy.

6.TOBY CHILDREN STUDY-UK Medical Research Council (MRC) – funded the TOBY Study also provided funding for expansion of the original trial with the aim of following the children who underwent therapeutic hypothermia upto the school age (6-7 years)

.This is a 4 year project 2009-2013.

The first families were allowed to participate in the trial by March 2010. The primary outcome of the study was to arrive at the frequency of survival with an IQ > or equal to 85(an IQ of 85 is 1 standard deviation below the standard.

The results of the study is yet to be published.ISRCTN 89547571. MREC NUMBER:10/H0711

ENDORSEMENTS AND RECOGNITION OF THERAPEUTIC HYPOTHERMIA FOR NEONATES:

1.In the special report in PAEDIATRICS- the official journal of the American Acadaemy of Paediatrics-formulated Neonatal Resuscitation:2010 American Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care-therapeutic hypothermia is mentioned as a treatment option.

2.NICE –National Institute of Health and Clinical Excellence and the British Association of Perinatal Medicine endorsed the application of therapeutic hypothermia in neonates in UK hospitals and suggests a registry.

3.Therapeutic hypothermia is widely used as a treatment option for asphyxiated neonates in countries and centres which initially participated in the trials. Anecdotally several other countries are also adopting cooling theraphy

THERAPEUTIC HYPOTHERMIA IN LOW COST SETTING – DEVELOPING COUNTRIES INCLUDING INDIA:

1.Therapeutic hypothermia using water bottles was tried as a treatment option in Uganda and was published in Lancet in September 2008. It reported a higher mortality.

2. A Feasibility trial was conducted in CMC vellore in India and was published in Indian Paediatrics in June 2011 and published online on November 2011.

some of the salient features of the above trial is presented here.

the ice gel packs and vaccine carriers was used

the adverse event reported in the study was

cardiac arrhythmia- nil

hypoglycemia (blood sugar <45 mg/dl) – 10%

hyperglycemia requiring insulin --15%

thrombocytopenia <100*10^3/ microlitre -- 25%

bleeding -- 5%

aposteatonecrosis -- 15%

hypoxemia -- 5%

hepatic dysfunction -- 5%

Oliguria –urine output -- < 0.5 ml/kg/h 5%

this trial also proved that the therapeutic hypothermia using low cost technology such as gel packs and vaccine carrriers instead of costlier servo control machine can be applied in a safe manner and it is also proved that the procedure is effective in maintaining the rectal temperature in the target range.

3. Robertson et al used water bottles for inducing therapeutic hypothermia

4.Horn et al used a servo control fan to maintain hypothermia.

Both the above studies shown that cooling can be done in a low resource setting in a low cost technology.

5.Both China and South Africa trials involved applying low cost technology in inducing hypothermia in neonates.

Mild hypothermia via selective head cooling as neuroprotective theraphy in term neonates with perinatal asphyxia: an experience from a single neonatal intensive care unit J Perinatology 2006:26:108-4 – Lin,Yu

6.JIPMER PONDICHERRY also involve in providing therapeutic hypothermia for perinatal asphyxia

therapeutic hypothermia using gel packs for term neonates with hypoxic ischaemic encephalopathy in resource – limited setting:- a randomized controlled trial by shruthi k.Bharadwaj and B.Vishnu Bhat arrived at a conclusion that therapeutic hypothermia using gel packs reduces the risk of death of developmental delay at 6 months of age in infants with HIE

Trial registration number: CTRI/2011/06/001780

Various molecular studies regarding the efficacy of therapeutic hypothermia was also conducted in Jipmer Pondicherry-estimation of malondialdehyde – product of lipid peroxidation, estimation of protein carbony levels – general oxidative stress-Nivedita, V Bhat et al. Indian Peditr 2010.77:515-517

Banupriya, V Bhat et al. Science Direct 2008.41:968-973

DNA based studies – comet length assay by Manoj, Rao, V Bhat et al Curr Pediatr Res 2011;15:121-125. this study concluded that comet length correlate well with HIE staging and severity

a randomized controlled trial-effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: concluded that therapeutic hypothermia reduces oxidative stress in term babies with perinatal asphyxia and is associated with better neurological outcome.

and reduction in oxidative stress could be an important mechanism by which therapeutic hypothermia works in HIE- Rojo Joy Femitha, P.Adhisivam, B.Vishnu Bhat, B.Zachariah Bobby

So clinical trials conducted by CMC Vellore and JIPMER Pondicherry prove to the point that inducing therapeutic hypothermia by a low cost technology such as gel packs and vaccine carriers is indeed possible and effective.

Now seminars, conferences and workshops were conducted in various places in India regarding therapeutic hypothermia for perinatal asphyxia.

ETHICAL AND CONTROVERSIES SURROUNDING THERAPEUTIC HYPOTHERMIA:

1. John and William discusses the efficacy and validity of therapeutic hypothermia in an article named “hot debate about a cool theraphy” in americal neonatal journal “NEOREVIEWS” - 2009. He finally concluded that therapeutic hypothermia can be offered as a treatment option probably and off protocol – cautiously
2. Sudin thayyil –“Brain cooling : are we ready for clinical trials in developing countries?” – an article appeared in Indian Paediatrics Journal June 2011discusses the possible adverse consequences of therapeutic hypothermia in newborns

OUTCOME IN PERINATAL ASPHYXIA:

The overall mortality in perinatal mortality reported in developed countries is about 20%

The probability of neurodevelopmental sequalae in surving newborns is approximately 30%

In stage II Hypoxic ischemic encephalopathy 80% have a normal neurodevelopmental outcome; and abnormal if symptoms more than5-7 days

In stage III Hypoxic ischemic encephalopathy about 50% die; remainder will have severe sequelae

Ambalavanan N et al: predicting prognosis in neonates with hypoxic ischemic encephalopathy; Paediatrics 2006;118:2084-2093 developed a scoring system and classification system in predicting the outcome of neonate suffered from perinatal asphyxia.

The above mentioned statistics were reported from developed countries. With intrauterine growth restriction, low birth weight, meconium stained liquors, poor resuscitation at birth, poor transport at birth complicating the picture in developing countries like India, mortality in perinatal hypoxia would be expected to be much higher.

The occurrence of seizures will increase the newborn's risk of cerebral palsy 50 to 70 fold. Seizures occurring within less than 12 hours of life have increased mortality and neurodevelopmental disability rates.

A report suggest that seizures are common in neonates undergoing therapeutic hypothermia – Yap V, Engel M, Takenouchi et al

Reccurent seizures and Electrographic seizures are also associated with poorer outcomes

Isoelectric or low voltage activity pattern of EEG portends a poorer prognosis in perinatal asphyxia.

Recovery of a normal background activity in EEG within 7 days of life is associated with a normal outcome.

A normal EEG is a predictor good outcome even in a comatose child

An abnormal MRI study in less than 3 days of life also portends a poorer prognosis. The abnormalities usually tend to regionalize around basal ganglia, thalami and the posterior limb of internal capsule

A persistent burst suppression pattern detected in electroencephalography even after 7 days of life also portends a poorer prognosis.

Microcephaly by 3 months of age and an abnormal neurological examination at 12 months of life portends a poorer prognosis. In one study it

was suggested that rate of regression in the head growth in less than 4 months of age would predict eventual microcephaly and poorer neurodevelopmental outcome at the age of 18 months.

Cordes I et al: Early prediction of the development of microcephaly after hypoxic ischemic encephalopathy in full term infants. Paediatrics 1994;93:703-707

Minor delay in reading, spelling ,arithmetic ,attention,memory were common in the survivors of perinatal asphyxia

EEG in newborn:

The Electroencephalogram or EEG is an important adjunctive tool in the assessment of infants with perinatal asphyxia.

It is a non invasive tool used for assessing the neonatal brain function.EEG is unique in a sense unlike other imaging procedures of the brain which provides only the anatomical details of the brain, it can provide functional status of the brain.

Several studies have proved the prognostic role of EEG in various disease states such as neonatal convulsion to perinatal asphyxia and traumatic birth injuries and haemorrhages.

As neonatal brain is rapidly evolving its function as a part of normal maturation EEG has a greater prognostic potential than any other diagnostic tool available to neonatologist.

EEG preffered in a sense that a newborn will present with a very narrow behavioural and clinical abnormalities compared adults with neurological abnormalities. Infantile spasm and its attended hypsarrythmia can suggested by specific EEG abnormalities in neonatal period prospectively.

EEG in newborns is applied in

1.diagnosis and treatment of seizures

2.evaluation of severity of cerebral dysfunction from primary neurologic disorders or systemic diseases.

3. Identification of specific neurological disorders

4. Determination of prognosis and long term neurological outcome

The normal neonatal EEG:

Interpretation of EEG in the newborn period is associated with its own inherent problems. EEG in a newborns differs from that of an adults certainly in many different ways.

For example gestational age should be taken into consideration while interpreting because EEG correlates with the gestational age of the infant

.Some maturational changes like delta brushes, frontal sharp transients and temporal theta bursts are to be considered as a normal variant

The most marked maturational changes occur between 24 weeks gestational age and 1 month after term. Hence in my study EEG was taken at the age of one month which would eliminate the maturational changes that would otherwise complicate the interpretation of EEG difficult.

. Also artefacts made by sudden movements, electrical equipments and the surrounding environment have to be considered. Ideally EEG in newborns should be supplemented with video recording of the events.

The abnormal neonatal electro encephalogram:

EEG in a neonate can manifest a wide range of abnormalities. Classifying the abnormalities in to diffuse and focal will makes the interpretation somewhat easier.

EEG in generally not diagnostic ie., in other words it is not very specific for particular disease process or causes. However birth asphyxia produces EEG abnormalities that resemble that of a diffuse encephalopathy pathology.EEG in neonates is usually described in terms of

1. the frequency of background activity
2. the symmetry
3. the synchrony between both hemispheres
4. the presence and absence of any abnormal patterns.

Prognostic significance of Neonatal Background EEG patterns were analysed in various studies.

EEG background patterns	Percent with favourable outcome
Isoelectric	0-5
Burst suppression	0 -15
Low voltage undifferentiated	14-3 0
Excessively discontinuous	40-5-
Diffuse slow activity	15-20

Gross asynchrony	10-20

INDICATION FOR EEG IN NEWBORNS:

Whenever the question arise regarding the abnormal neurological status of the neonate an EEG examination would serve a valuable adjuctive tool.

EEG is particularly valuable is the neonate is heavily sedated or been paralysed for various reason for example baby receiving fentanyl infusion while on mechanical ventilator support.

An EEG can greatly assist in discriminating between epileptic seizures and non epileptic events in the neonates. Non epileptic events like jitteriness is relatively common in neonates.

Hence EEG is a valuable situation in this regard.EEG is the only means of diagnosing the frequent subtle or subclinical seizures at present.

As already discussed determination of subclinical seizures became paramount importance when the association of seizures and the association of poor neurodevelopmental outcome was understood.

An EEG should be obtained early in the lifetime of a newborn who is at risk for developing seizures or encephalopathy because it provide a reference point for future comparisons.

Serial EEG instead of a single time EEG is a valuable prognostic tool as it can suggest the mode and timing of a brain insult to some extent.

Serial EEGS also useful in assessing the adequacy of treatment of seizures with anticonvulsants and follow up examinations.

An expanded version of EEG with additional gadgets including electrocardiogram, respiration assessment, oxygenation, extraocular movements and electromyogram would greatly supplement the interpretation.

Such a exhaustive or comprehensive multichannel monitoring will accurately disclose the various abnormalitie, will regionalize regional or hemispherical cerebral activies better, and will accurately stage neonatal sleep.

Various studies – including Tekgu et al showed that reduced montage- 9 electrodes instead of 10/20 standard electrodes will be sensitive enough to detect the seizures and grading of background EEG features in newborns.

Other EEG analysis techniques:

In recent days, several semi automated techniques for analyzing neonatal EEG have been developed'.

For example Two Channel EEGs, Spectral edge frequency, and Amplitude integerated EEG.

Amplitude integerated EEG:

aEEG or amplitude integerated EEG is used predominatly in neonates with perinatal hypoxia and its attended hypoxic ischaemic encephalopathy. This technology involves employing signal processing to rectify and integerate the EEG amplitudes with a compressed time scale.

aEEG is a sensitive tool in the assessment of severely abnormal patterns. The sensitivity for detecting seizures was fairly good (sensitivity 80%, specificity- 100%)

Spectral edge frequency:

This method is more appropriate for preterm neonates and it involves in tracking frequencies rather than amplitudes of the electrical signals .

The use of these new add on techniques require experience in the part of operator and interpretor and also frequent correlation with the routine EEGs.

Holmes and colleagues published an article in 1982 which concerns the EEG pattern assessment in perinatal asphyxiated neonates.

They analyzed the background patterns and paroxysmal activities and used to extrapolate these observation to predict outcome at an average age of 24

months in a blinded fashion. The timing of EEG varied ; anywhere between 5 days to a maximum of 14 days or 2 weeks .

A marginally abnormal or normal EEG is very reassuring. Because these neonates are unlikely to suffer from severe neurodevelopmental disability.

EEG was found to be more useful in infants who have moderate to severe encephalopathy.

The usefulness of EEG in infants who have hypoxic ischemic encephalopathy has been confirmed by multiple studies. some of them include

1. holmes g 1982
2. rowe j 1985
3. thornberg e 1984
4. hellstorm westas l 1995
5. van lieshout h 1995
6. Sinclair d 1995
7. toet m 1999
8. mcbride m 2000
9. biagioni e 2001
10. zeinstra e 2001

Shellaas RA described the sensitivity of amplitude integerated electroencephalography for seizure detection in the journal of Paediatrics 2007 journal

prolonged seizures by itself can exacerbate the damage to the brain in perinatal asphyxia- Wirrell –Paediatri Res 2001

Those seizures which have EEG-eletroencephalography findings have a poor neurological outcome-Neurology journal 2000

In the past 30 years there have been multiple studies reporting the neuro-developemental outcome in perinatal hypoxia. One particular literature was one that appeared in 1998 by Bohr and Greisen –it's a collection from 16 studies performed in various countries like Japan , US and from some of the countries in Europe . In the study 4% have mild forms of cerebral palsy and 10% have developmental delay.

PATHOPHYSIOLOGY BEHIND PERINATAL ASPHYXIA:

Normal labour will test the physiological reserve of a newborn baby. Surprisingly most of the babies are born with little oxygen reserve at birth. Many events are possibly related to this. they include

1.contraction of the uterus during labour may reduce the blood supply

2.some degree of cord compression is a possibility’

3. maternal dehydration and maternal alkalosis due to hyperventilation may possibly reduce the placental blood flow

4, increased oxygen consumption by both the mother and the fetus

Brief asphyxiating events produces

1.increase in the heart rate, elevation in blood pressure and increase in the central venous pressure with no ultimate change in the cardiac output. This is essentially increases the blood flow to vital organs such as brain, kidney- diving reflex.

2.severe but a short asphyxiating event such as placental abruption followed by caesarean section tends to produce a unique and characteristic pattern of neuronal injury that tend to localize to subcortical region and the brain stem nuclei

prolonged asphyxia produces more vivid biophysical changes:

1.loss of autoregulation of cerebral blood flow

2.increase in anaerobic metabolism and eventual energy failure in cells

3.fall in glycogen,ATP and phosphocreatine

4, prolonged asphyxiating events typically produces a diffuse injury – involving both cortical and subcortical structures

Subcellular events in asphyxia include:

1.failure of ion pumps

2.influx of sodium, chloride, calcium

3.excitatory neurotransmitters

4.increased apoptosis

5.increased oxidative stress

reperfusion of blood supply after a period of asphyxia worsen the amount of neuronal damage by increasing the oxygen free radicals

HOW DOES THERAPEUTIC HYPOTHERMIA WORK:

Exact mechanism of therapeutic hypothermia works still eludes the researchers.

various hypothesis suggested are

1. reducing the cellular metabolism
2. reducing the amount of excitotoxin
3. stabilizing the lipid membranes

4. reducing free radical injury
5. reducing the rate of apoptosis

THE CONCEPT OF WINDOW PERIOD IN THERAPEUTIC HYPOTHERMIA:

The notion that therapeutic hypothermia in newborn should be started in less than six hours of life and continued for next 72hours are derived from the experiences gained from the animal experiments in this field so far.

According to the experiments some of the neurons are going to die in the acute phase of asphyxia. But neuronal death continues for the next 2-3 days of postnatal life –secondary neuronal death. This secondary neuronal death is attributed to various reasons-

1.reperfusion injury

2.cerebral edema- which is worse during the first 36- 92 hours of life

3.calcium influx

4.free radical scavenging

5.increased apoptosis

once the clinical signs of these secondary neuronal damage such as seizures occurs hypothermia seems to be ineffective in preventing the subsequent inevitable death of further neurons. Thus there exist an window period – only during this early period therapeutic hypothermia seems to be effective in preventing neuronal deaths.

As mentioned the period of 72 hours is also extrapolated from animal studies.

As secondary neuronal death continues to occur upto 72 hours of life it is prudent to use hypothermia for that duration. apoptotic- necrotic continuum – recent animal models have shown that there is a prolonged period of delayed cell death due to apoptosis –Nakajima et al 2000

Why not greater than six hours? – This question in therapeutic hypothermia is a valuable one as greater number of newborns will be selected for cooling if the time period is extended. Only further clinical trials would help to clarify the issue.

Various neuroprotective agents apart from hypothermia have been suggested

These are

Caspase inhibitors

growth factors

deferoxamine

free radical inhibitors- allopurinol, vitamin e

nitric oxide synthase inhibitors

calcium channel blockers

GABA antagonists

erythropoietin

glycine’

phencyclidine

magnesium binding site

AMPA receptor antagonists

ETIOLOGIES OF HYPOXIC –ISCHEMIC CHANGES:

1. MATERNAL RISK FACTORS:

    hypertension

    hypotension

    infection- chorioamnionitis

    hypoxia from pulmonary or cardiac disorders

maternal vascular disorders

cocaine

abnormal placentation,

abruption

placental infarction

fibromyoma

rupture of the uterus

cord prolapsed, knot, compression

abnormalities of umbilical vessels

2.Fetal factors

infection

anaemia

hydrops

severe cardiac insufficiency

3.neonatal factors.

cyanotic congenital heart diseases

persistent pulmonary hypertention

cardiomyopathies

various forms of septic shock and cardiogenic shock

SEIZURES IN HYPOXIC ISCHEMIC ENCEPHALOPATHY:

1. occur in about 50% of neonates with HIE
2. usually starts less than twenty four hours of life
3. seizures indicate that the severity is moderate or severe
4. may be of the types- subtle, tonic or clonic
5. jitteriness may be occasionally confused with
6. often subclinical- only recorded by EEG
7. EEG remains the gold standard in diagnosing
8. compromise ventilation, oxygenation
9. associated with poor developmental outcome
10. EEG is required to detect electroclinical dissociation- subclinical seizures after starting anticonvulsants

ANTICONVULSANTS IN PERINATAL HYPOXIA:

1. phenobarbitone is the initial drug of choice

2. phenytoin may be added
3. fos phenytoin is associated with less hypotensive effect
4. benzodiazepines – third line drugs
5. levetiracetam – used recently

LONG TERM ANTICONVULSANT MANAGEMENT:

1. anticonvulsants should be stopped when the clinical examination and Electroencephalography indicate that the newborn is no longer having seizures
2. weaning should in reverse order of the drugs introduced
3. some favour withdrawal phenobarbitone shortly before discharge
4. some favour continued treatment for 1-6 months
5. those with persistent neurological deficit and those with an abnormal EEG have high risk for developing recurrent seizures.

NEUROLOGICAL MARKERS OF BRAIN INJURY IN PERINATAL HYPOXIA:

1. CK-BB
2. S-100
3. neuron specific enolase

4. urine markers

VARIOUS FORMS OF INJURY IN HIE

1. FOCAL
2. MULTIFOCAL
3. WATERSHED INJURY
4. SELECTIVE NEURONOL INJURY

   focal and multifocal injuries are associated with cystic changes

   watershed injuries- following severe hypotension –inbetween arterial territories – injury to parieto-occipital cortex

   selective neuronal –CA1 neurons of hippocampus is highly sensitive to hypoxia

   status marmoratus – necrosis of thalamic nuclei and basal ganglia is a variant of selective neuronal loss

MULTIPLE ORGAN INVOLVEMENT IN PERINATAL HYPOXIA:

1. One or more organ involvement occur in more than 80% of neonates with perinatal hypoxia.

2. central nervous system is the most common organ to be involved – about 70%
3. the next common organ to be involved is kidney -45%
4. pulmonary, cardiac and gastrointestinal system are the next common organs to be involved

Acute perinatal asphyxia scoring system

- used to predict multiple organ involvement in birth asphyxia
- it components are
- 1. 5 minute apgar score
- 2. umbilical artery base deficit
- 3. fetal heart rate monitor tracing
- multiple organ involvement is more likely if the score is more than 6.

Gluckman Pd and Azoparrdi they led the landmark study of therapeutic hypothermia and it was published in the lancet journal in 2005.

Sankaran et al work on whole body hypothermia for neonates suffering from perinatal hypoxia was published in New England journal of medicine- 2005

ACOG task force analysed the pathogenesis and pathophysiology behind perinatal asphyxia leading on to cerebral palsy.

EEG during early periods of perinatal asphyxia can predict the neurodevelopmental outcomes at the age of 2 years –Murray in Paediatrics 2009

The spectrum of clinical entities and predicting the outcomes in perinatal hypoxia is discussed by Walter C.Allan – Neoreviews 2002- American academy of paediatrics- state that the studies regarding the outcome in perinatal asphyxia is best guided by clinical assessment and EEG and both are readily available.

An infant beginning to seek the nipple before the end of the second week of life – a optimistic sign towards the prognosis of the baby- Walter C Allan

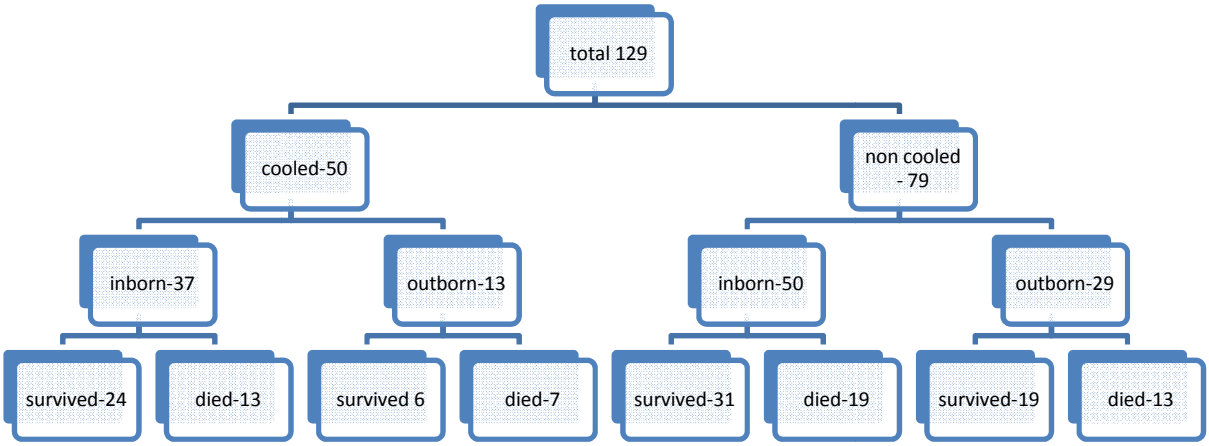
Outcome studies are disappointing for magnetic resonance imaging – likelihood ratios are not better than Electroencephalogram or evoked potentials.

OBSERVATION AND RESULTS:

1. Total number of babies admitted in our unit with moderate to severe encephalopathy in the period of 7 months(from may 2012 to November 2012) is 129
2. out of 129 babies 50 babies received therapeutic hypothermia as a treatment-

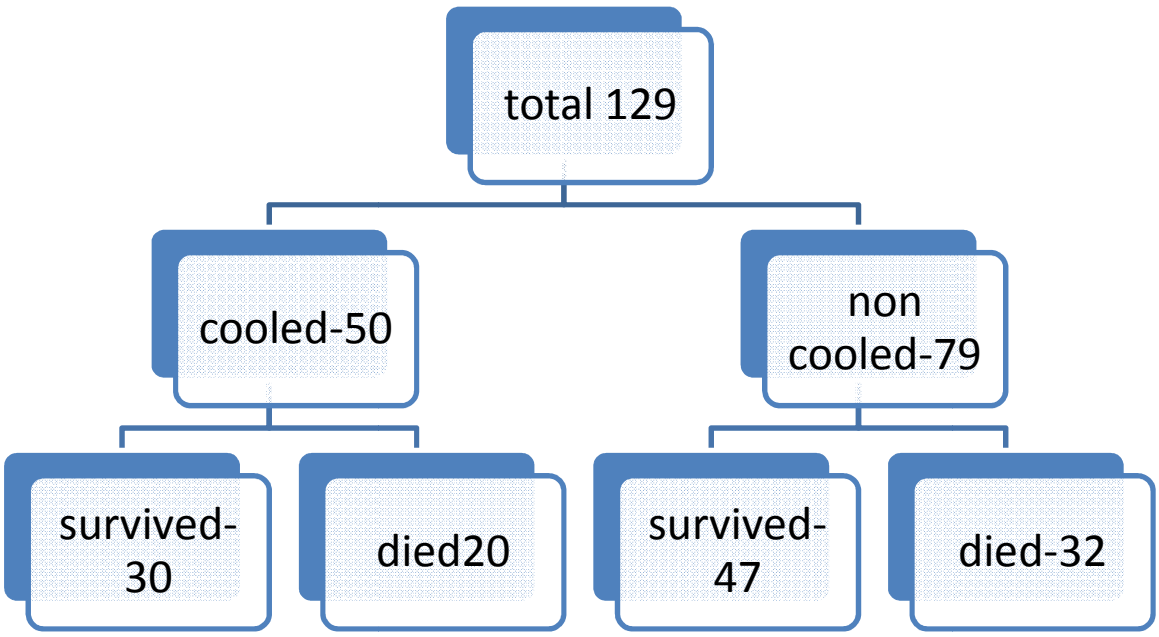
   It is represented in the flow diagram as follows

   figure1.



Among these 129 neonates 87 were delivered in our institution and 42 were referred from other hospitals.(fig.1 and fig.2). Of the total 129 neonates 50 received therapeutic hypothermia as a treatment modality. Every neonate was considered for therapeutic hypothermia treatment. Refusal of consent, arrival at greater than 6hrs of life or inability to initate cooling at 6 hrs of life, babies showing features of encephalopathy at greater than 6 hrs of life would fall in to non cooling group. In those babies who satisfy the inclusion criteria cooling will be started immediately as much as possible.

figure 2.



1. Of the total number 129 neonates 52 died- representing a combined mortality rate of 40.31%
2. Out of the 50 babies who underwent hypothermia as a treatment modality 20 neonates died – a mortality rate of 40%
3. Out of the 79 babies who were not cooled – not received therapeutic hypothermia and managed in a conventional manner 32 neonates have died – a mortality rate of 40.5%
4. Out of 37 inborn babies who underwent cooling 13 babies died – a mortality rate of 35.13%

5. Out of 13 outborn babies who underwent cooling 7 died – a mortality rate of 53.84%
6. Among the babies who underwent therapeutic hypothermia 2 babies died of pneumonia. These two babies have a prolonged hospital stay, with need for prolonged ventilator support compared to other babies who died without pneumonia. The duration of hospital stay was about 40 days, and 21 days for the abovesaid babies. In both of these babies blood cultures were negative. But in both of these babies Endo tracheal aspirate given for culture was positive for klebsillae which was sensitive to piperacillin tazobactam and ciprofloxacin. So pneumonia as a contributory factor accounts for 10% of the mortality in the cooled babies. One of these babies required glucose infusion at 6 mg/kg/min for hypoglycemia for 2 days.
7. Out of the 20 babies died in the cooling cohort two baby had pulmonary haemorrhage as a complication. This would account for 10% of the mortality in the cooled group. One of these babies developed apnea on day 1 life and required mechanical ventilator support on day 1 of life
8. Out of the 20 babies died in the cooling cohort one baby developed cellulitis of right upper limb and died of refractory shock.
9. Out of the 20 babies died in the cooling cohort one baby was found to have pneumothorax during admission. This baby was transported in

the ambulance and there is history of displacement of Endotracheal tube during the transport and the need for bag and mask ventilation during the transport. The pneumothorax was mild and was resolved on day 1 of life. Baby required ventilator support since admission and baby died of refractory shock on day 5 of life.

10. Out of the 20 babies died in the cooling cohort 3 babies were found to have associated thrombocytopenia – a prevalence of 15%
11. Out of the 6 babies who developed pneumonia in the cooling cohort 2 babies died. That would amount to a mortality rate of 33% for pneumonia in these cohort.
12. Out of the 20 babies died in the cooling cohort 6 were stage III. one baby with stage III HIE survived. This amount to mortality rate of 85.7% mortality in stage III HIE.

ANANLYSIS OF MORTALITY:

Mortality among cooled and Non cooling babies

TABLE 1.

	No of Babies Cooled	Non Cooling Group	Total
Survived	30 (60%)	47 (59.49%)	77
Died	20 (40%)	32 (40.51%)	52
Total	**50**	**79**	**129**

P value = 0.954 > 0.05 there is no difference in the mortality among cooled and non cooled babies

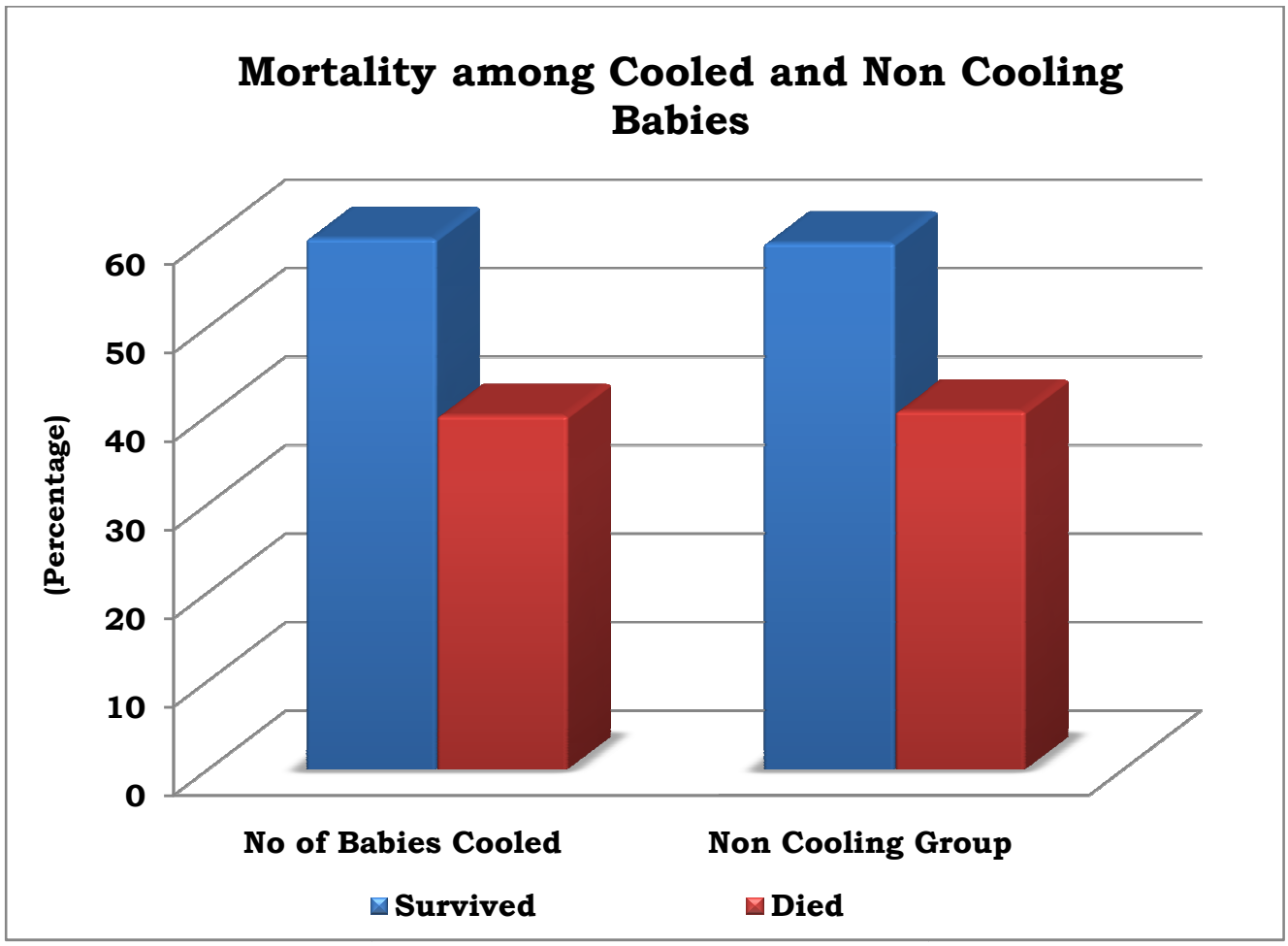

Mortality among Cooled and Non Cooling Babies
(Percentage)
60
50
40
30
20
10
0
No of Babies Cooled
Non Cooling Group
Survived
Died

FIGURE 3:

:

Mortality among inborn and out born babies of babies who underwent therapeutic hypothermia

TABLE 2:

	In born	Out born	Total
Survived	24 (64.86%)	6 (46.15%)	30
Died	13 (35.14%)	7 (53.85%)	20
Total	37	13	50

P value = 0.236 > 0.05 there is no difference in the mortality among cooled and non cooled babies

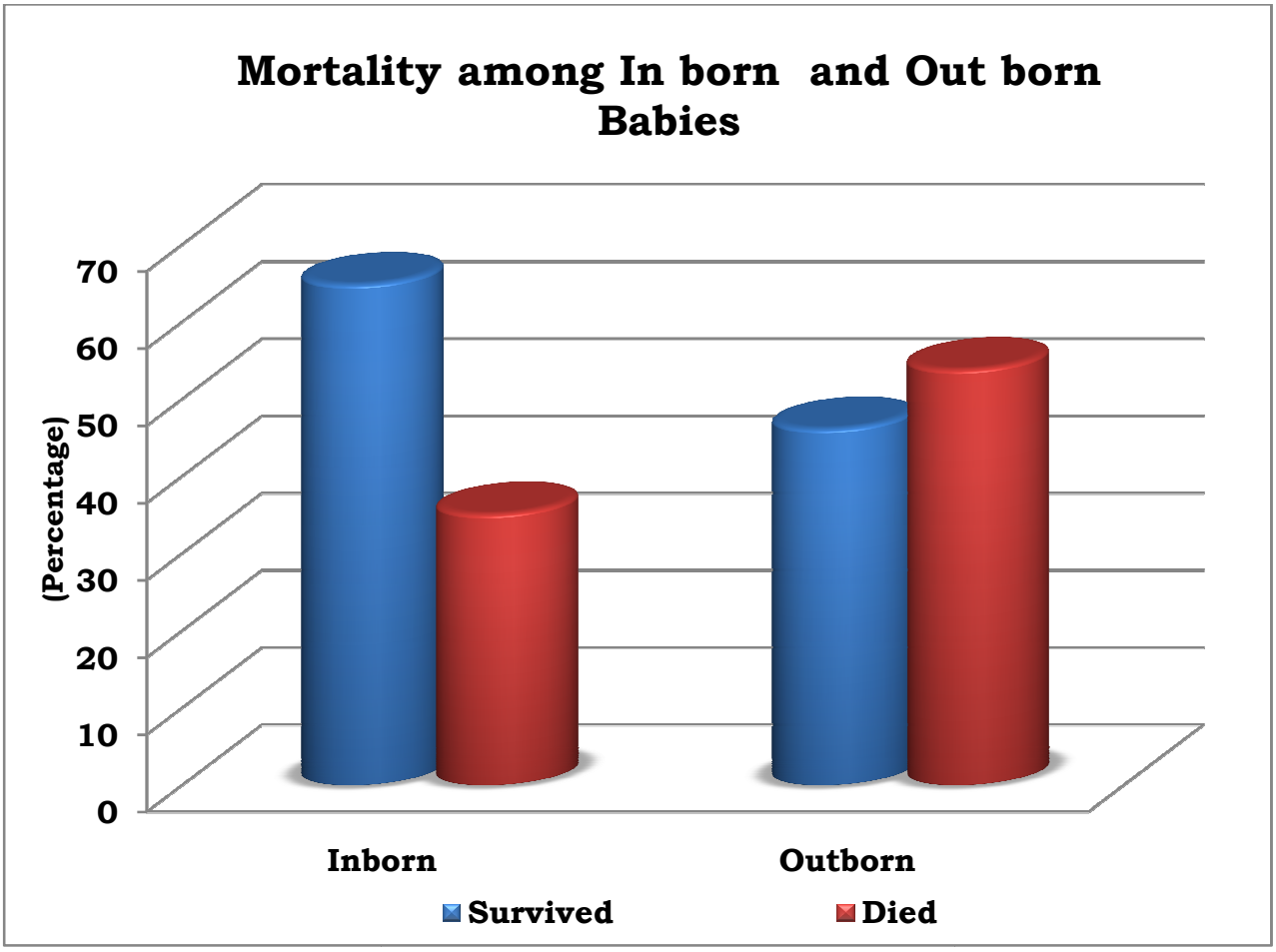

Mortality among In born and Out born Babies
(Percentage)
70
60
50
40
30
20
10
0
Inborn
Outborn
Survived
Died

FIGURE 4:

ANALYSIS OF MORBIDITY PATTERNS OF BABIES WHO UNDERWENT THERAPEUTIC HYPOTHERMIA:

TABLE 3:

Morbidity	No .of Patients	Percentage
Bleeding-rectal	1	2
Cellutis,thrombocy	1	2
Pneumonia	6	12
Pul haemorrhage	2	4
Sc fat necrosis	2	6.6
Sepsis	2	4
Thrombocytopenia	2	4

1. PERCENTAGE OF PNEUMONIA IN THE COOLED GROUP : Out of 50 babies who underwent therapeutic hypothermia 6 babies developed pneumonia during the hospital course – an incidence of about 12% . As already mentioned out of the 6 babies with pneumonia 2 babies died. Out of the 4 babies with pneumonia and survived 2 babies were blood culture positive for klebsillae.
2. Thus 2 babies were positive for blood culture out of 50 cooled babies and none of the babies who died in the cooling cohort have developed positive blood culture. This would amount to incidence of blood culture positive sepsis in the cooling cohort to 4%

3. Out of 30 babies who survived in the cooling cohort 2 babies developed subcutaneous fat necrosis with an estimated incidence of 6.66% in the alive babies

4. Out of 30 babies who survived in the cooling cohort one baby developed rectal bleeding on day 3 of life- at the completion of cooling .rectal bleeding lasted for 2 days and the baby was transfused fresh frozen plasma twice.

5. Out of 30 babies who survived in the cooling cohort one baby required exchange transfusion for hyperbilurinemia. Exchange transfusion was done on 5 th day of life. This baby showed features of HIE during early hours of life – well before the clinical evidence of hyperbilurinemia

6. Out of 30 babies who survived in the cooling cohort one baby required umbilical vein cathetarisation during the hospital course as there is difficulty in securing a peripheral iv line.

7. Out of 30 babies who survived in the cooling cohort all babies underwent neuroimaging modality by ultrasound cranium at approximately one week of life. Ultrasound cranium was normal in all the babies who survived.

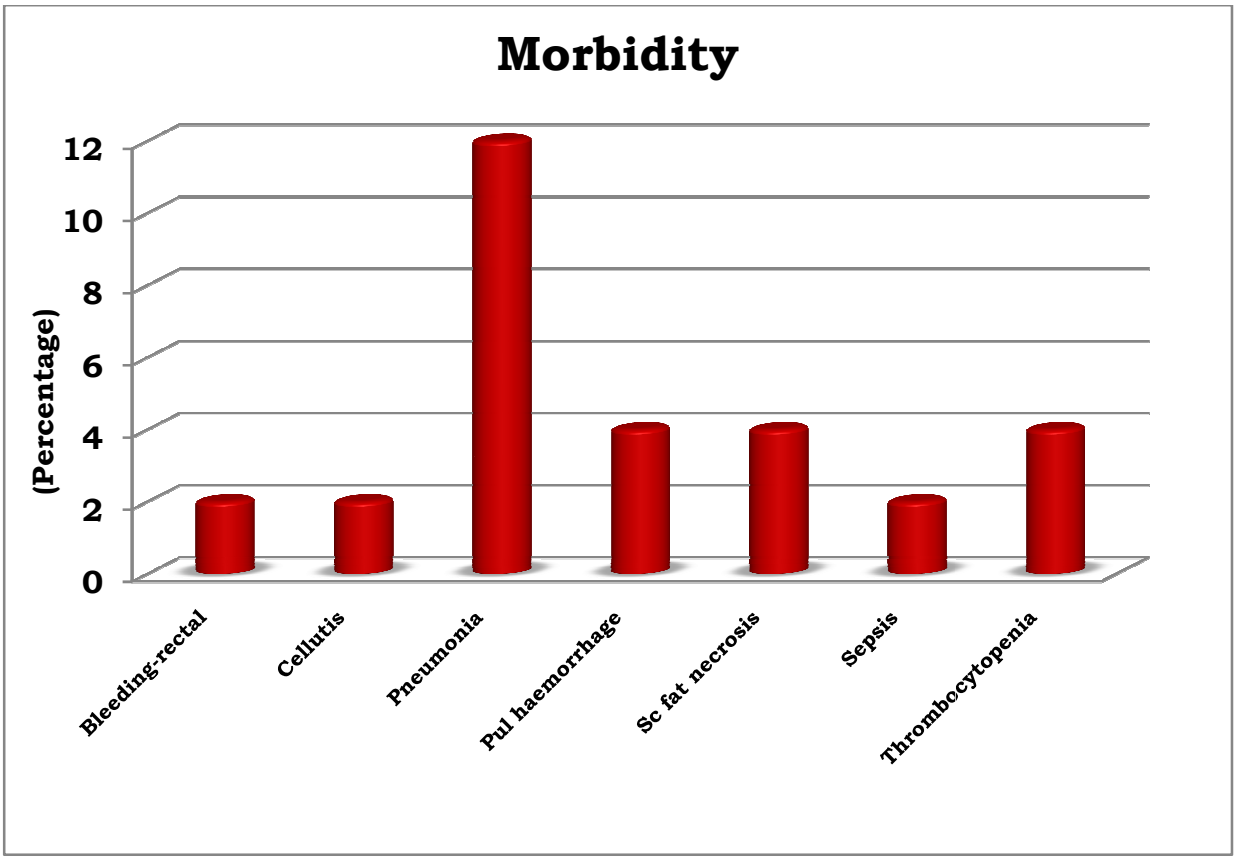

Morbidity
(Percentage)
12
10
8
6
4
2
0
Bleeding-rectal
Cellutis
Pneumonia
Pul haemorrhage
Sc fat necrosis
Sepsis
Thrombocytopenia

FIGURE 5:

Gravida	No	Percentage
Primi	40	80
G2	6	12
G3	2	4
G4	2	4

TABLE 4:

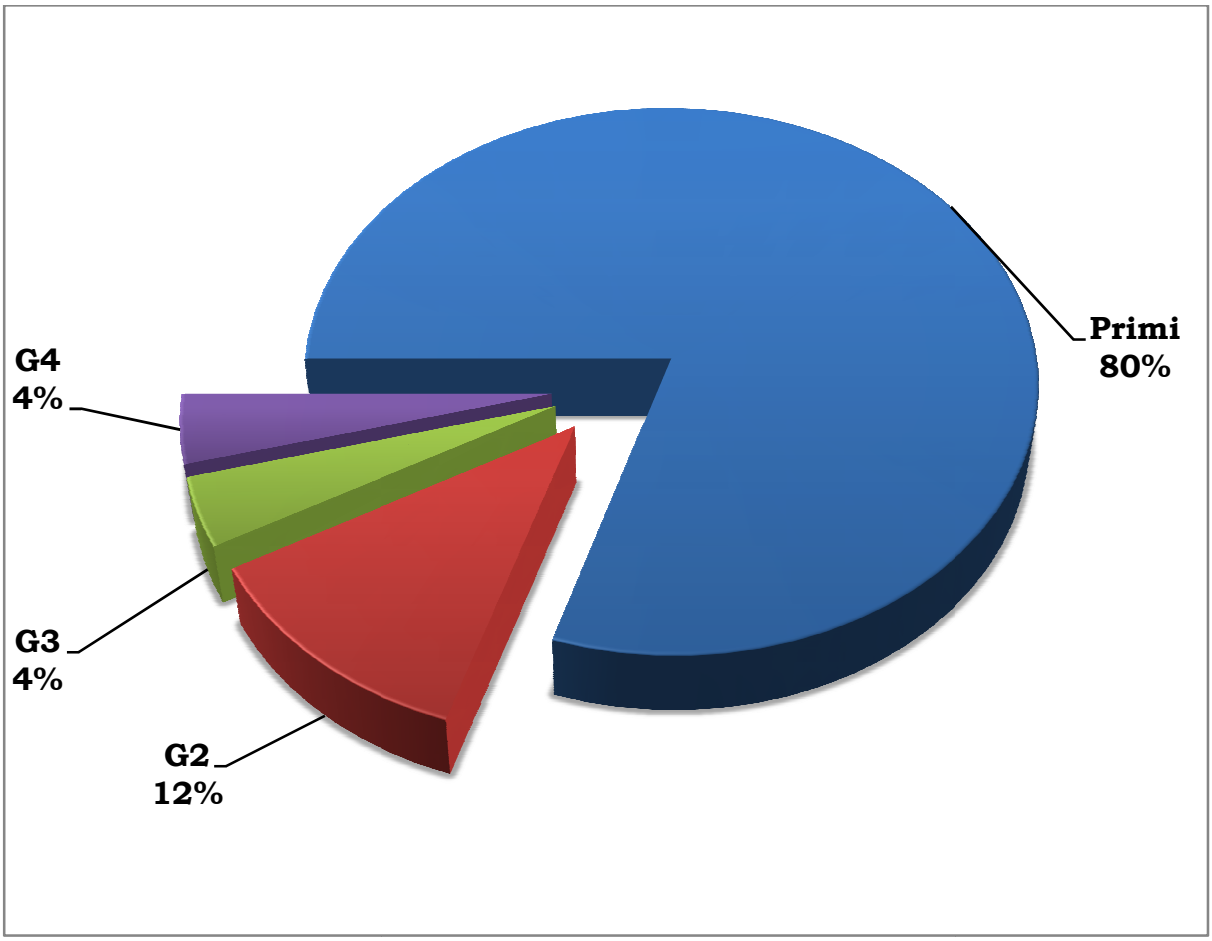


FIGURE 6:

thus babies born to primi mothers contribute to majority share of moderate to severe encephalopathy babies who were recruited for cooling theraphy. out of 50 babies meconium stained liquour was present in 10 babies – about 20%

TABLE 5:

Nature of Delivery	No. of patients	Percentage
Vaginal	43	86
LSCS	2	4
Forceps	5	10
Total	50	100

DELIVERING BY FORCEPS IS A SIGNIFICANT RISK FACTOR FOR HIE – AS IT IS INHERENT TO THE NATURE OF THE PROBLEM IN THAT FORCEPS IS USED IN DIFFICULT LABOUR

FIGURE 7:

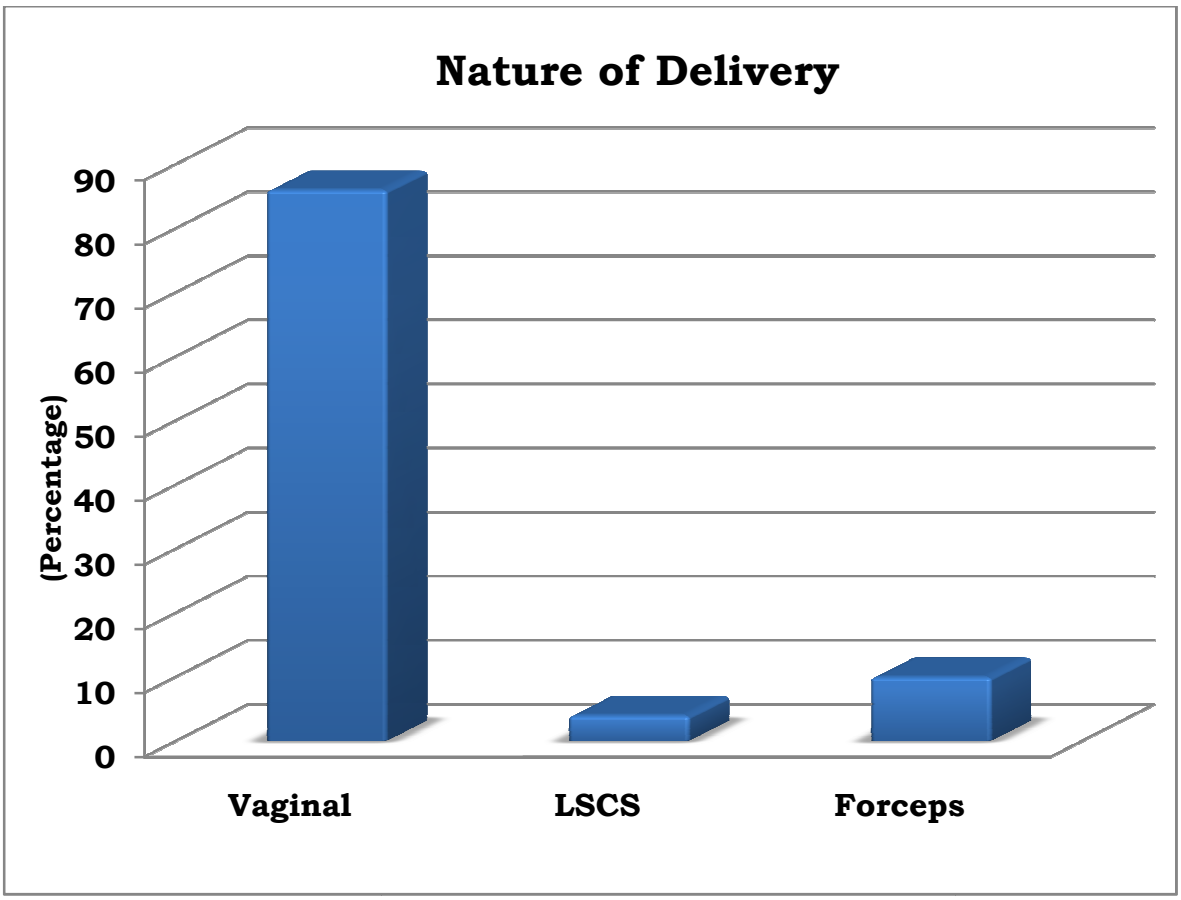

Nature of Delivery
(Percentage)
90
80
70
60
50
40
30
20
10
0
Vaginal
LSCS
Forceps

TABLE 6:

	Yes	Percentage
O2	31	62
CPAP	29	58
Ventilator	25	50
Phenobarbitone	46	92
Phenytoin	11	22
Midazolm	2	4
Dopamine	36	72
Dobutamine	26	52
Adrenaline	5	10

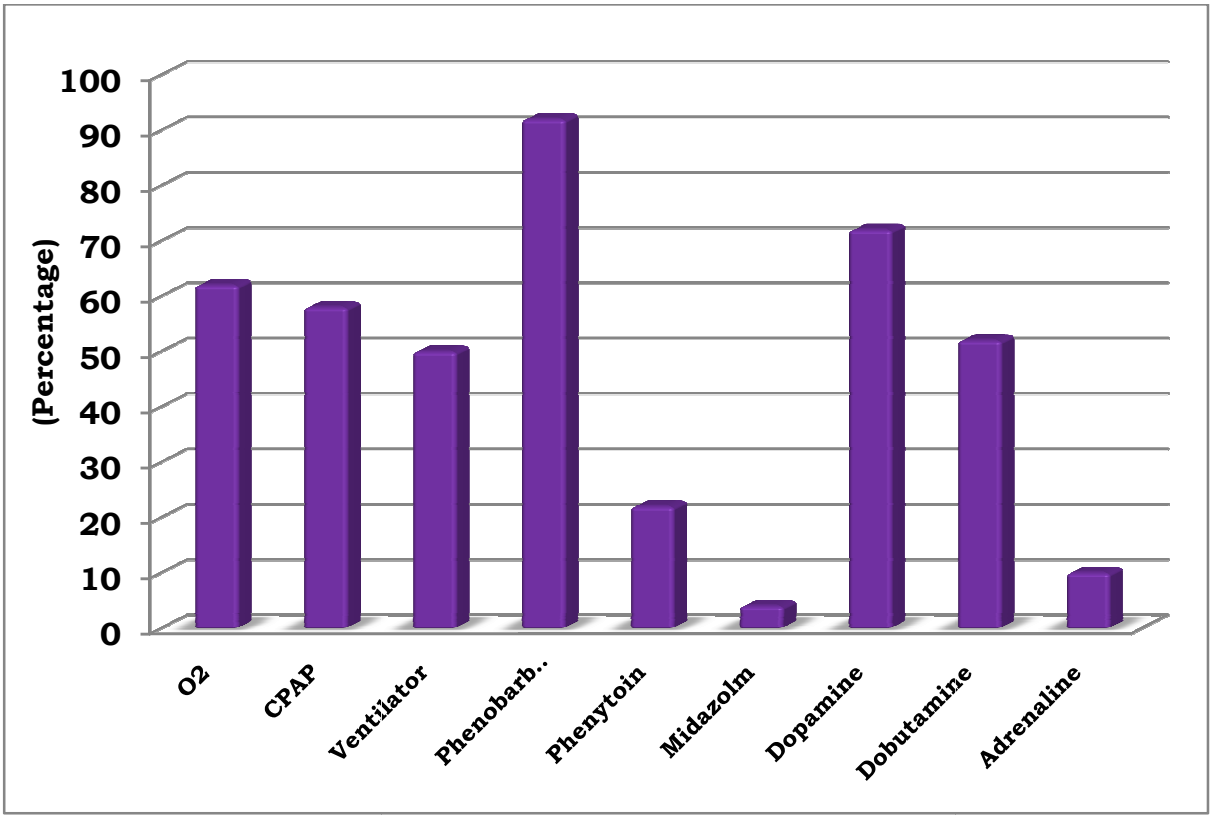


FIGURE 8:

THUS WE CAN SEE THAT THERE IS NEED FOR MECHANICAL VENTILATOR SUPPORT IN NEARLY HALF OF NEONATES WITH MODERATE TO SEVERE ENCEPHALOPATHY

ANTICONVULSANTS WERE USED IN THE MAJORITY THUS HIE STAGE II REPRESENTS THE MAJOR PORTION OF THE GROUP

THERE IS RELATIVELY HIGHER USAGE OF INOTROPIC SUPPORT IN THE COHORT OF COOLED BABIES

TABLE 7: THUS THERE IS SIGNIFICANT PERCENTAGE OF NEONATES WHO UNDERWENT THERAPEUTIC HYPOTHERMIA SHOWS ABNORMALITY IN EEG

Babies survived	**No of babies with EEG Taken**	**EEG Normal**	**No of babies with Abnormal EEG**

30	22	17 (77.3%)	5 (23.7%)

Out of 30 babies survived 8 babies are not turn for the EEG. EEG was taken for 22 babies in 5 babies EEG were abnormal.

	No of babies with EEG Taken	**EEG Normal**	**No of babies with Abnormal EEG**
In born	17	13 (76.5%)	4 (23.5%)
Out born	5	4 (80%)	1 (20%)

TABLE 8:

20 % of the Out born babies having abnormal EEG and 23.5% of the In born babies having Abnormal EEG

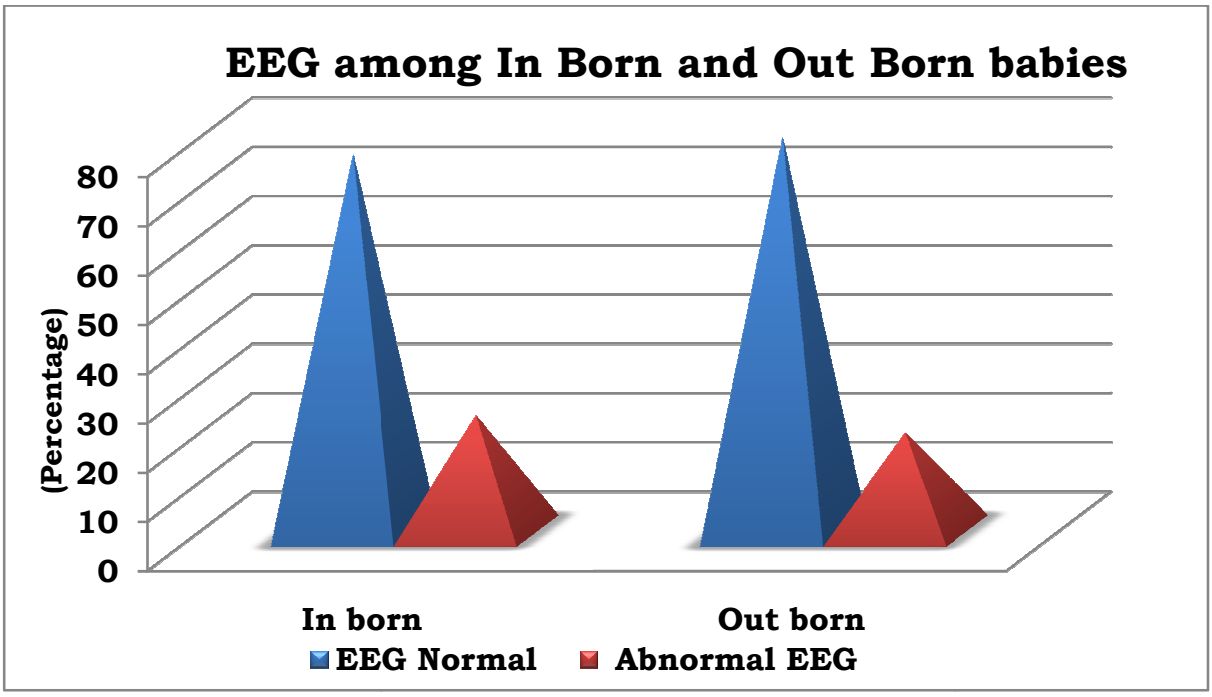


FIGURE 9:

TABLE 9:

	EEG Normal		EEG Abnormal	
	N	**Mean ± S.D**	**N**	**Mean ± S.D**
Head of circumference	11	-1.453 ± 0.751	4	-0.842 ± 1.320
weight	11	-1.783 ± 1.585	4	-1.018 ± 0.917
Days of Hospitalisation	17	10.76 ± 3.832	5	11.6 ± 7.73

TABLE 10:

	No of patients	**Mean**	**Standard Deviation**
Birth Weight	45	2.816	0.367
Days of Hospitalisation	50	9.38	6.872

TABLE 11:

Comparison of Head Circumference between Cooled and Well babies

Babies	No of patients	Mean	Standard Deviation	P value
Cooled babies	17	-1.174	0.230	
				0.014
Well Babies	19	-0.285	0.266	

Average Head circumference of cooled babies is -1.174 and well babies is -0.285 with the p value <0.05 there is a significant difference in head circumference between both the babies

Comparison of weight between Cooled and Well babies TABLE 12:

Babies	No of patients	Mean	Standard Deviation	P value
Cooled babies	17	-1.385	0.268	
				0.035
Well Babies	19	-0.588	0.245	

Average Head circumference of cooled babies is -1.385 and well babies is -0.588 with the p value <0.05 there is a significant difference in head circumference between both the babies

DISCUSSION:

1. MORTALITY:

From the data we can observe a relatively higher mortality rate for moderate to severe encephalopathy overall than that reported in developed countries.

This can be attributed to possible high incidence of associated meconium stained liquour in considerable proportions and relatively higher incidence of bacterial sepsis and pneumonia in these babies.

The overall mortality rate reported in developed countries is about 20%. The mortality rate are comparatively higher in developing countries like India.

In our study the overall mortality rate for both stage II and stage III Hypoxic ischemic encephalopathy was 40% .

It should be noted that stage I Hypoxic ischemic encephalopathy babies were not included in this study that would otherwise reduced the overall mortality.

The mortality rate among cooled and non cooled groups were similar – around 40% and difference if any was statistically significant.

Thus it can be concluded that therapeutic hypothermia in a level II nicu setting by using low cost technology does not alter the mortality rate of Hypoxic encephalopathy babies.

The mortality rate was considerably higher in those babies referred to the hospital than the babies who were born at the hospital-53.85% and 35.15 % respectively – although the statistical analysis showed that difference was insignificant – the probable explanation would be relative difference in the resuscitation at birth in peripheral hospital and condition prevailing during transport.

These factors can adversely affect the physiological state of the newborn during admission affecting the mortality thereby.

MORBIDITY:

The commonest morbidity among the neonates with moderate to severe encephalopathy was pneumonia. The incidence of pneumonia was higher in this population about 12%.

Among the 6 cases of pneumonia 2 were blood culture positive for klebsillae and 2 were ET aspirate culture positive for klebsillae. This could possibly attributed to relatively higher incidence of early onset sepsis and hospital acquired infection in this group of neonates

Bleeding in the form of pulmonary haemorrhage and rectal bleeding occurred in significant propotion of cases in cooled group. Most of the babies in the cooling group showed prolonged coagulation profiles and majority of them received fresh frozen plasma.

Bleeding also occurred in non cooling group- about 3.6%. Hence there is no difference in the rate of bleeding tendency between cooled and non cooled group.

Out of the 30 babies who survived 2 babies were found to have subcutaneous fat necrosis. Similar rates were reported in other

study regarding therapeutic hypothermia in neonates. These 2 babies were otherwise normal clinically.

EEG:

As we can see from the results that significant propotion about 22% (nearly one fourth) of the neonates who underwent therapeutic hypothermia showed abnormalities.None of the 30 babies who survived have seizures or developmental delay as a concern by the parents.

All the babies with abnormal EEG were normal by neurological examination and normal by developmental assessment by Denver Developmental Screening Test- DDSTII

It should be noted only 23 patients out of 30 patients turned out for EEG examinations.

Developmental Assessment:

Developmental Assessment using denver developmental screening test was carried out in all the babies who underwent thera -peutic hypothermia in the month of December by two sessions . Each babies was examined at approximately 10 minutes time.

All the babies who was examined were having normal developmental screening test. Only 22 out of 30 survivors turned out for the screening test. This proves to the fact that most of HIE II babies have a normal neurodevelopmental outcome.

ANTHROPOMETRIC MEASUREMENTS:

All the babies on follow up found to lag behind in terms of weight gain and the head circumference compared to similar age group infants found in well baby clinics in our institution

This may be partly explained by the nutritional deprivation during the hospital course, failure of lactation in the mother due to failure to initiate lactation immediately after birth.

Expressing the breast milk in the mothers of babies with perinatal hypoxia would probably help to sustain the lactation in the mother.

CONCLUSION:

There is significant proportion of neonates who underwent therapeutic hypothermia showed abnormalities in the electroencephalogram at the age of one month. Repeated neurological examination and serial EEG and possibly MRI would aid in the management of this subgroup of neonates.

REFERENCES:

1. Govt of India (2008), Sample registration system. Statistical Report 2007, report no.2 of 2008. Ministry of Home Affairs, New Delhi.
2. Govt of India (2005), Sample registration system. Statistical Report 2003, report no.2 of 2005.
3. www.who.int – world health organization – health statistics- countries – India
4. Holzer, Michael. "Mild Hypothermia to Improve the Neurologic Outcome After Cardiac Arrest." New England Journal of Medicine. (2002) Vol. 346, No. 8.
5. Polderman, Kees H. "Application of therapeutic hypothermia in the ICU." Intensive Care Med. (2004) 30:556-
6. "Surgeons use cold to suspend life". *BBC News*. 27 September 2010.
7. Therapeutic Hypothermia After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation - Nolan et ...
8. Sessler, Daniel. "Thermoregulation and Heat Balance." Therapeutic Hypothermia. Ed. Mayer, Stephen and Sessler, Daniel. Marcel Decker: New York, 2005.
9. Edwards, AD; Brocklehurst, P; Gunn, AJ; Halliday, H; Juszczak, E; Levene, M; Strohm, B; Thoresen, M et al. (2010). "Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data". *BMJ (Clinical research ed.)* **340**: c363.
10. Bernard, Stephen et al. "Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia." New England Journal of Medicine. (2002) Vol. 346, No. 8.
11. "Therapeutic Hypothermia". eMedicine. 29 June 2010.
12. Krieger, Derk. et al."Cooling for Acute Ischemic Brain Damage." American Heart Association. May 25, 2001, pg. 1847-1854

13. Schwab, S. et al. "Moderate Hypothermia in the Treatment of Patients with Severe Middle Cerebral Artery Infarction." American Heart Association. July 31, 1998, pg. 2461-2466
14. Florian B, Vintilescu R, Balseanu AT, Buga A-M, Grisk O, Walker LC, Kessler C, Popa-Wagner A (2008). "Long-term hypothermia reduces infarct volume in aged rats after focal ischemia".*Neuroscience Letters* **438** (2): 180–185. .
15. Jess Arcure BS, MSC; Eric E Harrison MD. (2009). "Review Article of the Use of Early Hypothermia in the Treatment of Traumatic Brain Injuries". *JSOM Summer 2009 Volume 10 Edition 1* **10**.
16. Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD001048..
17. Dringer, Michael et al. "Elevated body temperature independently to increased length of stay in neurological intensive care unit patients." Critical Care Medicine. 2004 Vol. 32, No. 7, pg. 1489-1495
18. Kammersgaard, L.P. et al. "Admission Body Temperature Predicts Long-Term Mortality After Acute Stroke American Heart Association. March 12, 2002, pg. 1759-1762.
19. Ginsberg, Myron et al. "Combating Hyperthermia in Acute Stroke." American Association. November 10, 1997, pg. 529-534.
20. Polderman, Kees. "Induced hypothermia and fever control for prevention and treatment of neurological injuries." Lancet. 2008; 371: 1955–69
21. Taccone, F; Donadello, K, Beumier, M, Scolletta, S (20 May 2011). "When, where and how to initiate hypothermia after adult cardiac arrest.". *Minerva anestesiologica*.
22. Adler, Jerry. "Back From the Dead." Newsweek. July 23, 2007
23. Calver, Patty. "The Big Chill." RN. (2005) Vol. 68, No.
24. Schwab, Stefan et al. "Feasibility and Safety of Moderate Hypothermia After Massive Hemisphere Infarction." American Heart Association. June 4, 2001, pg. 2033-2035.
25. Hoedemaekers, Cornelia et al. "Comparison of different cooling methods to induce and maintain normo- and hypothermia in ICU patients: a prospective intervention study." Critical Care. 11:R91. August 24, 2007..
26. Diringer, Michael. "Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system." Crit Care Med. Vol. 32, No. 2. 2004.

27. Flemming, Kerstin. "Comparison of external and intravascular cooling to induce hypothermia in patients after CPR." GMS Ger Med Sci 2006; 4:Doc04.
28. Hinz, Jose. "Effectiveness of an Intravascular Cooling Method Compared With a Conventional Cooling Technique in Neurologic Patients." J Neurosurg Anesthesiol. Vol. 19, No. 2. April 2007.
29. Keller, Emanuela et al. "Endovascular cooling with heat exchange catheters: a new method to induce and maintain hypothermia." Intensive Care Med. 29: 939-943. May 1, 2003.
30. Holzer, Michael et al. "Efficacy and Safety of Endovascular Cooling After Cardiac Arrest." Stroke. 37:000-000. July 2006.
31. Pichorn, Nicolas et al. "Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest usuing an endovascular cooling system." Critical Care. Vol 11, No. R71. June 28, 2007.
32. Schwab, Stefan et al. "Feasibility and Safety of Moderate Hypothermia After Massive Hemisphere Infraction."
33. Haugk, Moritz et al. "Feasibility and efficacy of new non-invasive cooling device in post resuscitation intensive care medicine." Resuscitation (2007) 75, 76-81
34. [Simosa, H. et al. "Increased Risk of Deep Venous Thrombosis with Endovascular Cooling in Patients with Traumatic Head Injury."]
35. Castren M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation 2010;122:729–36.
36. Castren M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation 2010;122:729–36
37. Busch H, Eichwede F, Födisch M, et al. Safety and Feasibility of nasopharyngeal evaporative cooling in the emergency department setting in survivors of cardiac arrest. Resuscitation 2010;81: 943-949
38. Deakin C, Nolan J, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2010. Section 4. Adult Advanced Life Support. Resuscitation. 81; 2010: 1305-1352
39. Holden, Mary et al. "Clinically Induced Hypothermia: Why Chill Your Patient?" Advanced Critical Care. (2006) Vol. 17, No. 2, pg. 125-132.

40. Clumpner M, Mobley J. Raising the dead: Prehospital hypothermia for cardiac arrest patients may improve neurological outcome and survival to discharge. EMS 37(9): 52-60, Sep 2008.
41. ^ "The DigniCap™ scalp cooling system" (Press release). Dignitana AB. Retrieved 2012-02-12.
42. ^ "FDA Approves Novel Device That Prevents or Reduces Brain Damage in Infants" (Press release). U.S. Food and Drug Administration. December 20, 2006. Retrieved 2012-02-12.
43. Gluckman, PD; Wyatt, JS; Azzopardi, D; Ballard, R; Edwards, AD; Ferriero, DM; Polin, RA; Robertson, CM et al. (2005). "Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial". *Lancet* **365** (9460): 663–70.
44. Gunn, A; Gluckman, PD; Wyatt, JS; Thoresen, M; Edwards, AD. (2005). "Selective head cooling after neonatal encephalopathy". *Lancet* **365** (9471): 1619–20. doi:10.1016/S0140-6736(05)66505-1.
45. Shankaran, S; Laptook, A; Wright, LL; Ehrenkranz, RA; Donovan, EF; Fanaroff, AA; Stark, AR; Tyson, JE et al. (2002). "Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants". *Pediatrics* **110**(2 Pt 1): 377–85. doi:10.1542/peds.110.2.377. PMID 12165594.
46. Shankaran, S; Laptook, AR; Ehrenkranz, RA; Tyson, JE; McDonald, SA; Donovan, EF; Fanaroff, AA; Poole, WK et al. (2005). "Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy". *N. Engl. J. Med.* **353** (15): 1574–84. doi:10.1056/NEJMcps050929.PMID 16221780.
47. Kirpalani, H; Barks, J; Thorlund, K; Guyatt, G. (2007). "Cooling for neonatal hypoxic ischemic encephalopathy: do we have the answer?". *Pediatrics* **120** (5): 1126–30.doi:10.1542/peds.2006-2776. PMID 17974750.
48. Hutchison, JS; Ward, RE; Lacroix, J; Hebert, PC; Barnes, MA; Bohn, DJ; Dirks, PB; Doucette, S et al. (2008). "Hypothermia therapy after traumatic brain injury in children". *N. Engl. J. Med.* **358**(23): 2447–56. doi:10.1056/NEJMoa0706930. PMID 18525042.
49. Clifton, GL; Miller, ER; Choi, SC; Levin, HS; McCauley, S; Smith, KR; Jr, J. Paul; Wagner Jr, FC et al. (2001). "Lack of effect of induction of hypothermia after acute brain injury". *N. Engl. J. Med.***344** (8): 556–63. doi:10.1056/NEJM200102223440803. PMID 11207351.

50. Higgins, RD; Raju, TN; Perlman, J; Azzopardi, DV; Blackmon, LR; Clark, RH; Edwards, A; Ferriero, D et al. (2006). "Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop". *J. Pediatr* **148** (2): 170–5. doi:10.1016/j.jpeds.2005.12.009.
51. Azzopardi, DV; Strohm, B; Edwards, AD; Dyet, L; Halliday, HL; Juszczak, E; Kapellou, O; Levene, M et al. (2009). "Moderate hypothermia to treat perinatal asphyxial encephalopathy". *N Engl J. Med* **361** (14): 1349–58. doi:10.1056/NEJMoa0900854. PMID 19797281.
52. Jacobs, S; Morley, CJ; Inder, TE; ICE Collaboration (2011). "Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial.".*Arch Pediatr Adolesc Med* **165** (8): 692-700. doi:10.1001/archpediatrics.2011.43.PMID 21464374.
53. Edwards, AD (2009). "The discovery of hypothermic neural rescue therapy for perinatal hypoxic-ischemic encephalopathy". *Seminars in pediatric neurology* **16** (4): 200–206.doi:10.1016/j.spen.2009.09.007. PMID 19945654.
54. Siesjo, BK; Katsura, K; Kristian, T. (1995). "The biochemical basis of cerebral ischemic damage". *Journal of neurosurgical anesthesiology* **7** (1): 47–52. doi:10.1097/00008506-199501000-00009. PMID 7881240.
55. Siesjö, BK (1981). "Cell damage in the brain: a speculative synthesis". *Journal of Cerebral Blood Flow and Metabolism* **1** (2): 155–85. doi:10.1038/jcbfm.1981.18. PMID 6276420.
56. Taylor, DL; Edwards, AD; Mehmet, H. (1999). "Oxidative metabolism, apoptosis and perinatal brain injury". *Brain Pathol* **9** (1): 93–117. doi:10.1111/j.1750-3639.1999.tb00213.x.PMID 9989454.
57. Roth, Simon C.; Edwards, A. David; Cady, Ernest B.; Delpy, David T.; Wyatt, John S.; Azzopardi, Denis; Baudin, Jenny; Townsend, Jan et al. (2008). "RELATION BETWEEN CEREBRAL OXIDATIVE METABOLISM FOLLOWING BIRTH ASPHYXIA, AND NEURODEVELOPMENTAL OUTCOME AND BRAIN GROWTH AT ONE YEAR". *Developmental Medicine & Child Neurology***34** (4): 285–95. doi:10.1111/j.1469-8749.1992.tb11432.x.
58. Robertson, NJ; Cox, IJ; Cowan, FM; Counsell, SJ; Azzopardi, D; Edwards, AD. (1999). "Cerebral intracellular lactic alkalosis persisting months after neonatal encephalopathy measured by magnetic resonance

spectroscopy". *Pediatr. Res.* **46** (3): 287–96.doi:10.1203/00006450-199909000-00007. PMID 10473043.
59. Siesjö, BK; Elmér, E; Janelidze, S; Keep, M; Kristián, T; Ouyang, YB; Uchino, H (1999). "Role and mechanisms of secondary mitochondrial failure". *Acta neurochirurgica. Supplement* **73**: 7–13. PMID 10494335.
60. Northington, FJ; Ferriero, DM; Graham, EM; Traystman, RJ; Martin, LJ. (2001). "Early Neurodegeneration after Hypoxia-Ischemia in Neonatal Rat Is Necrosis while Delayed Neuronal Death Is Apoptosis". *Neurobiol. Dis.* **8** (2): 207–19. doi:10.1006/nbdi.2000.0371.PMID 11300718.
61. McDonald, J; Johnston, MV (1990). "Physiological and pathophysiological roles of excitatory amino acids during central nervous system development". *Brain Research Reviews* **15** (1): 41–70. doi:10.1016/0165-0173(90)90011-C. PMID 2163714.
62. Wang, X.; Carlsson, Y.; Basso, E.; Zhu, C.; Rousset, C. I.; Rasola, A.; Johansson, B. R.; Blomgren, K. et al. (2009). "Developmental Shift of Cyclophilin D Contribution to Hypoxic-Ischemic Brain Injury". *Journal of Neuroscience* **29** (8): 2588–96.doi:10.1523/JNEUROSCI.5832-08.2009. PMC 3049447. PMID 19244535.
63. Northington, FJ; Ferriero, DM; Flock, DL; Martin, LJ (2001). "Delayed neurodegeneration in neonatal rat thalamus after hypoxia-ischemia is apoptosis". *Journal of Neuroscience* **21** (6): 1931–8. PMID 11245678.
64. Gill, Ramanjit; Soriano, Marc; Blomgren, Klas; Hagberg, Henrik; Wybrecht, Remy; Miss, Marie-Therese; Hoefer, Sandra; Adam, Geo et al. (2002). "Role of Caspase-3 Activation in Cerebral Ischemia-Induced Neurodegeneration in Adult and Neonatal Brain". *Journal of Cerebral Blood Flow & Metabolism*: 420. doi:10.1097/00004647-200204000-00006.
65. Bona, E; Andersson, AL; Blomgren, K; Gilland, E; Puka-Sundvall, M; Gustafson, K; Hagberg, H (1999). "Chemokine and inflammatory cell response to hypoxia-ischemia in immature rats".*Pediatric research* **45** (4 Pt 1): 500–9. doi:10.1203/00006450-199904010-00008.PMID 10203141.
66. Hedtjärn, M; Leverin, AL; Eriksson, K; Blomgren, K; Mallard, C; Hagberg, H (2002). "Interleukin-18 involvement in hypoxic-ischemic brain injury". *Journal of Neuroscience* **22** (14): 5910–9.
67. Boutin, H; Lefeuvre, RA; Horai, R; Asano, M; Iwakura, Y; Rothwell, NJ (2001). "Role of IL-1alpha and IL-1beta in ischemic brain damage". *Journal of Neuroscience* **21** (15): 5528–34..

68. Hedtjärn, Maj; Mallard, Carina; Iwakura, Yoichiro; Hagberg, Henrik (2005). "Combined Deficiency of IL-1β18, but Not IL-1αβ, Reduces Susceptibility to Hypoxia-Ischemia in the Immature Brain". *Developmental Neuroscience* **27** (2–4): 143–.
69. Ferriero, DM (2004). "Neonatal brain injury". *The New England Journal of Medicine* **351** (19): 1985–95.
70. Erecinska, M; Thoresen, M; Silver, IA. (2003). "Effects of hypothermia on energy metabolism in mammalian central nervous system". *J Cereb. Blood Flow Metab* **23** (5): 513–30.
71. Amess, PN; Penrice, J; Cady, EB; Lorek, A; Wylezinska, M; Cooper, CE; D'souza, P; Tyszczuk, L et al. (1997). "Mild hypothermia after severe transient hypoxia-ischemia reduces the delayed rise in cerebral lactate in the newborn piglet". *Pediatric research* **41** (6): 803–8.
72. Gunn, AJ; Gunn, TR; Gunning, MI; Williams, CE; Gluckman, PD. (1998). "Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep". *Pediatrics* **102**(5): 1098–106.
73. Smith, SL; Hall, ED. (1996). "Mild pre- and posttraumatic hypothermia attenuates blood–brain barrier damage following controlled cortical impact injury in the rat". *J. Neurotrauma* **13** (1): 1–9..
75. Nakashima, K; Todd, MM. (1996). "Effects of hypothermia on the rate of excitatory amino acid release after ischemic depolarization". *Stroke* **27** (5): 913–8
76. Globus, MY; Alonso, O; Dietrich, WD; Busto, R; Ginsberg, MD. (1995). "Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia". *J. Neurochem* **65** (4): 1704–11.
77. Akisu, M; Huseyinov, A; Yalaz, M; Cetin, H; Kultursay, N. (2003). "Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia". *Prostaglandins Leukot. Essent. Fatty Acids* **69** (1): 45–50. .
78. **E**dwards, AD; Yue, X; Squier, MV; Thoresen, M; Cady, EB; Penrice, J; Cooper, CE; Wyatt, JS et al. (1995). "Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia". *Biochem. Biophys. Res. Commun.* **217** (3): 1193–9
79. Xu, L; Yenari, MA; Steinberg, GK; Giffard, RG. (2002). "Mild hypothermia reduces apoptosis of mouse neurons in vitro early in the cascade". *J Cereb. Blood Flow Metab* **22** (1): 21–8.

80. Zhang, Z; Sobel, RA; Cheng, D; Steinberg, GK; Yenari, MA. (2001). "Mild hypothermia increases Bcl-2 protein expression following global cerebral ischemia. Brain Res. Mol". *Brain Res.* **95**: 75–85.
81. Edwards, AD; Brocklehurst, P; Gunn, AJ; Halliday, H; Juszczak, E; Levene, M; Strohm, B; Thoresen, M et al. (2010). "Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data". *BMJ (Clinical research ed.)* **340**: c363.
82. Shankaran, S; Pappas, A; McDonald, SA; Vohr, SR; Hintz, SR; Yolton, K; Gustafson, KE; Leach, TM et al. (2012). "Childhood outcomes after hypothermia for neonatal encephalopathy".*New England Journal of Medicine* **366** (22): 2085-92.
83. Guillet, R; Edwards, AD; Thoresen, M; CoolCap Trial Group (2011). "Seven- to eight-year follow-up of the CoolCap trial of head cooling for neonatal encephalopathy.". *Pediatr Res* **71** (2): 205-9.
84. Rutherford, M; Ramenghi, LA; Edwards, AD; Brocklehurst, P; Halliday, H; Levene, M; Strohm, B; Thoresen, M et al. (2010). "Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial". *Lancet neurology* **9** (1): 39–45. doi:10.1016/S1474-4422(09)70295-9.PMC 2795146. PMID 19896902.
85. Robertson, NJ; Nakakeeto, M; Hagmann, C; Cowan, FM; Acolet, D; Iwata, O; Allen, E; Elbourne, D et al. (2008). "Therapeutic hypothermia for birth asphyxia in low-resource settings: a pilot randomised controlled trial". *Lancet* **372** (9641): 801–3. doi:10.1016/S0140-6736(08)61329-X. PMID 18774411.

86. Whole Body Cooling in Newborn Infants with Perinatal Asphyxial Encephalopathy in a Low Resource Setting:
A Feasibility Trial

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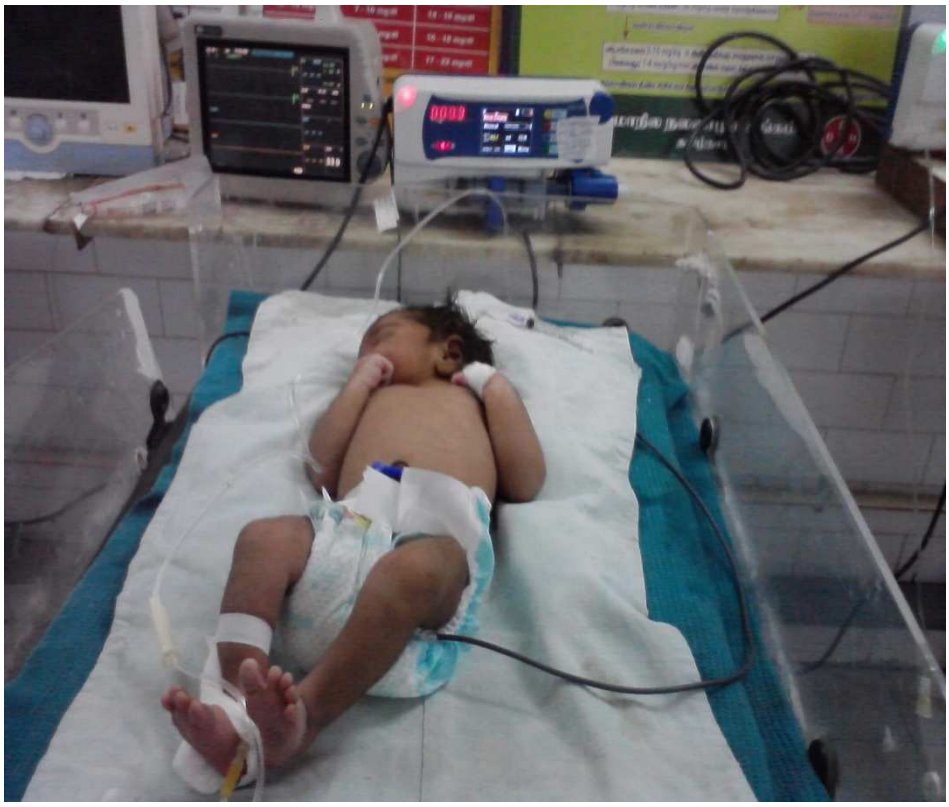
87. Edwards A, Brocklehurst P, Gunn A, Halliday H, Juszczak E, Levene M, *et al.* Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic

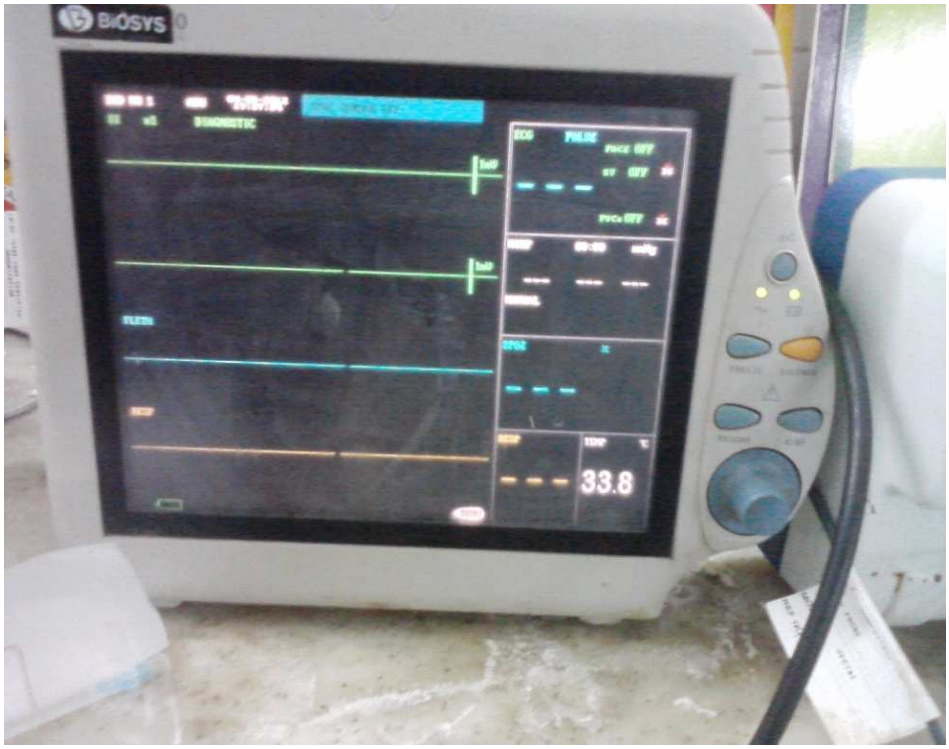
ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ. 2010;340:C363.
88. Lawn JE, Kinney M, Lee AC, Chopra M, Donnay F, Paul VK, *et al.* Reducing intrapartum-related deaths and disability: Can the health system deliver? Int J Gynaecol Obstet. 2009;170:S123-42.
89. Jacobs SE, Stewart M, Inder T, Doyle LW, Morley CJ. ICE: the Australian cooling trial for hypoxic-ischemic encephalopathy—in hospital outcomes. Proceedings of the Hot Topics in Neonatology Conference. Washington, DC, 2008.
89. Merchant RM, Abella BS, Peberdy MA, Soar J, Ong ME, Schmidt GA, *et al.* Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Crit Care Med. 2006;34:S490-4.
90. Zhou WH, Cheng GQ, Shao XM, Liu XZ, Shan RB, Zhuang DY, *et al*. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in China. J Pediatr. 2010;.157:367-72.
91. Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, *et al.* Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet.
92. Biagioni E, Mercuri E, Rutherford M, et al. Combined use of electroencephalogram and magnetic resonance imaging in fullterm neonates with acute encephalopathy. *Pediatrics.* 2001; 107:461–468
93. Bohr L, Greisen G. Prognosis after perinatal asphyxia in full-term infants. A literature review. *Ugeskr Laeger*. 1998;160:2845–2850

1.BABY HAVING CONVULSION



2.BABY UNDER THERAPEUTIC HYPOTHERMIA

3. USE OF GEL PACKS IN THERAPEUTIC HYPOTHERMIA



4. RECTAL TEMPERATURE BEING MONITORED VIA RECTAL PROBE

S.NO	NAME OF THE PATIENT	IP NO	SURVIVED/DEAD	MOTHER DETAILS	NATURE OF DELIVERY	APGAR	BIRTH WEIGHT	SEX	INBORN/OUTBORN	O2	CPAP	VENTILATOR	PHENOBARBITONE	PHENYTOIN	MIDAZOLAM	DOPAMINE	DOBUTAMINE
1	B/O THILAGA	16506	S	G2 - PIH	VAGINAL	3--4	2.25	M	I	Y	N	N	Y	N	N	N	N
2	B/O SASIKALA	18863	S	G3	VAGINAL	3--5	3.6	F	I	Y	Y	Y	Y	N	N	Y	Y
3	B/O CHITRA	19268	S	PRIMI	VAGINAL		3	M	O	N	N	N	Y	N	N	N	N
4	B/O UMAMAHESWARI	20396	S	PRIMI- CORD -NECK	VAGINAL	4--5	2.9	M	I	Y	N	N	Y	N	N	N	N
5	B/O JEYALAKSHMI	20969	S	PRIMI	VAGINAL	4--6	2.3	M	I	Y	N	N	Y	N	N	Y	N
6	B/O HEMAVATHY	31449	S	PRIMI	VAGINAL	4--5	3.2	M	I	Y	N	N	Y	N	N	Y	Y
7	B/O JAMUNARANI	32202	S	PRIMI	VAGINAL		2.75	F	O	Y	N	N	Y	Y	N	N	N
8	B/O ANGAMMAL	32799	S	PRIMI	VAGINAL	3--5	3.2	M	I	Y	Y	N	Y	N	N	N	N
9	B/O THAMARAISELVI	33723	S	PRIMI	VAGINAL		3	M	O	N	N	N	Y	Y	N	N	Y
10	B/O RADHIKA	33927	S	PRIMI	VAGINAL	3--6	2.8	F	I	Y	Y	Y	Y	N	N	Y	N
11	B/O SHARMILA	35154	S	PRIMI	VAGINAL		3.5	M	O	Y	Y	N	Y	Y	N	N	N
12	B/O NANDHINI	36445	S	SHORT PRIMI	VAGINAL	2--4	2.625	M	I	N	N	N	Y	N	N	Y	Y
13	B/O SEETHALAKSHMI	36907	S	PRIMI	VAGINAL	4--6	2.8	F	I	Y	Y	N	Y	Y	N	Y	N
14	B/O MUNIYAMMAL	40499	S	PRIMI	VAGINAL	4--5	2.8	M	I	Y	Y	N	Y	N	N	Y	N
15	B/O KANAGA	29051	S	PRIMI	VAGINAL	NA	2.8	M	O	Y	Y	Y	Y	Y	Y	N	N
16	B/O SELVI	30577	S	G4	VAGINAL	4--5	2.93	M	I	Y	Y	N	Y	N	N	Y	N
17	B/O PARVATHY	31200	S	PRIMI	VAGINAL	4--6	2.39	M	I	Y	Y	Y	Y	N	N	Y	N
18	B/O LAVANYA	35394	S	PRIMI	VAGINAL	NA	2.905	M	O	N	N	N	Y	N	N	Y	N
19	B/O MALAR	41089	S	G4+MSAF	LSCS	5--7	3	M	I	Y	N	N	Y	N	N	N	N
20	B/O PRIYA	41063	S	PRIMI/PIH	VAGINAL	3--5	2.5	F	I	Y	Y	N	Y	N	N	N	N
21	B/O SREEDEVI	42773	S	PRIMI	FORCEPS	5--6	2.8	M	I	Y	Y	Y	Y	Y	N	Y	N
22	B/O SANGEETHA	42512	S	G2	VAGINAL	4--6	3.8	F	I	Y	Y	N	Y	N	N	N	Y
23	B/O EZZHILRANI	43129	S	PRIMI	VAGINAL	3--6	3.15	M	I	Y	N	N	Y	N	N	Y	N
24	B/O GNAMMAL	44753	S	PRIMI	VAGINAL	4--6	3.05	M	I	Y	N	N	Y	N	N	Y	N
25	B/O MOHANA	44939	S	PRIMI	VAGINAL	5--7	2.15	F	I	Y	N	N	Y	N	N	Y	N
26	B/O SANDHYA	44218	S	PRIMI	VAGINAL	NA	2.7	M	I	Y	N	N	Y	N	N	N	N
27	B/O SARIDHA	45317	S	PRIMI	VAGINAL	NA	2.4	M	I	Y	Y	N	Y	Y	N	N	Y
28	B/O PARIMALA	42938	S	PRIMI	FORCEPS	5--6	3	M	I	Y	Y	N	Y	N	N	Y	N
29	B/O PREMA	37120	S	G2	VAGINAL	5--6	3.3	M	I	Y	Y	N	Y	Y	N	Y	N
30	B/O SHANTHI	46075	S	G2	VAGINAL	5--7	3.2	F	I	Y	N	N	Y	N	N	N	N
31	B/O NEELA	16350	D	PRIMI	VAGINAL	NA	2.75	M	O	Y	Y	Y	Y	N	Y	Y	Y
32	B/O AMBIKA	18158	D	PRIMI+MSAF	VAGINAL	2--4	2.8	M	I	N	N	Y	Y	N	N	Y	Y
33	B/O SANGEETHA	18838	D	PRIMI	VAGINAL	3--5	2.6	M	I	Y	Y	Y	N	N	N	Y	Y
34	B/O MALINI	16423	D	PRIMI	VAGINAL	3--5	2.85	F	I	N	N	Y	Y	N	N	Y	Y
35	B/O VIJAYA	23408	D	G2	VAGINAL	2--4	2.5	F	I	N	N	Y	Y	N	N	Y	Y
36	B/O DHATCHAYANI	18940	D	PRIMI	FORCEPS	2--4	2.5	M	I	Y	Y	Y	Y	N	N	Y	Y
37	B/O LAKSHMI	25688	D	PRIMI	VAGINAL	4--5	2.7	F	I	N	N	Y	Y	N	N	Y	Y
38	B/O SATHYA	24073	D	PRIMI+MSAF	VAGINAL	NA	2.3	M	I	N	Y	Y	Y	N	N	Y	Y
39	B/O PADMAVATHY	23570	D	PRIMI	VAGINAL	NA	2.9	F	I	N	Y	Y	N	N	N	Y	Y
40	B/O AIYSHA	30473	D	G3	VAGINAL	4--4	2.5	M	I	N	N	Y	Y	N	N	Y	Y
41	B/O CHITRA	32163	D	PRIMI	LSCS	4--5	2.7	M	I	N	Y	Y		N	N	Y	Y
42	B/O SANGEETHA	28918	D	PRIMI	VAGINAL	4--5	2.87	M	I	Y	Y	Y	Y	N	N	Y	Y
43	B/O SATHYA	36916	D	PRIMI	FORCEPS	3--6	2.47	M	I	N	Y	Y	y	N	N	Y	Y
44	B/O VIJI	38868	D	PRIMI	VAGINAL	NA	2.8	F	O	Y	Y	Y	Y	Y	N	Y	Y
45	B/O ELAVARASI	38500	D	PRIMI	VAGINAL	NA	2.3	F	O	N	Y	Y	Y	Y	N	Y	Y
46	B/O SUMATHI	38433	D	PRIMI	VAGINAL	NA	3.45	M	O	N	N	Y	Y	Y	N	Y	Y
47	B/O NEELAKODI	40951	D	PRIMI	VAGINAL	NA	3.065	M	O	N	Y	Y	Y	N	N	Y	Y
48	B/O SUDHA	43523	D	PRIMI	VAGINAL	NA	2.9	M	I	N	Y	Y	Y	N	N	Y	Y
49	B/O ROJA	44145	D	G2	FORCEPS	NA	2.75	F	I	N	Y	Y	Y	N	N	Y	Y
50	B/O SHARMILA	35377	D	PRIMI+MSAF	VAGINAL	2--3	2.6	F	O	N	Y	Y	Y	N	N	Y	Y

S.NO	ADRENALINE	MORBIDITY	DAYS OF HOSPITALISATION	HEAD CIRCUMFERENCE	WEIGHT	DENVER II	EEG	EEG-COMMENTS	OTHER REMARKS
1	N		11					REFUSED	
2	N		20				NORMAL		
3	N		8	-1.41	-0.41	PASS	NORMAL		
4	N		9	-1.28	-2.22	PASS	ABNORMAL	RIGHT FRONTO PARIETAL SPIKES	
5	N	BLEEDING-RECTAL	6			PASS	NORMAL		RECTAL BLEEDING
6	N	PNEUMONIA	18	-1.23	0.11	PASS	NORMAL		
7	N		8	-2.57	-2.43	PASS	NORMAL		C/O DROOLING OF SALIVA
8	N		11	-0.7	-0.39	PASS	NORMAL		
9	N		8	-1.82	-1.98	PASS	NORMAL		
10	N	SC FAT NECROSIS	9	0.98	-0.53	PASS	ABNORMAL	BIL EPILEPTIFORM ACTIVITY	
11	N		5	-2.15	-0.12	PASS	ABNORMAL	BIL EPILEPTIFORM ACTIVITY	
12	N	SEPSIS	11	-2.25	-5.41	PASS	NORMAL		CULTURE POSITIVE FOR KLEBSILLA
13	N		11			PASS	NORMAL		
14	N		9			PASS	NORMAL		C/O EPISODIC UPWARD GAZE
15	N	PNEUMONIA	20						UVC WAS USED
16	N		13			PASS	NORMAL		SINGLE CAFÉ-U-LAIT SPOT
17	N	PNEUMONIA	25				ABNORMAL		CULTURE POSITIVE FOR KLEBSILLA
18	N		12				NORMAL		EXCHANGE TRANSFUSION FOR HYPERBILURUNEMIA
19	N	SC FAT NECROSIS	8						ABSCONDED
20	N		10	-2.3	-2.91	PASS	NORMAL		
21	N		5						
22	N		8	0.52	0.09	PASS			
23	N		8						DISCHARGE AT REQUEST
24	N		10	-0.36	-0.73	PASS	NORMAL		
25	N		6	-1.63	-2.21	PASS	NORMAL		
26	N		9	-1.56	-2.23	PASS			
27	N		18	-1.81	-3.13	PASS			
28	N		14	-1.28	-2.49	PASS	NORMAL		
29	N		10	-0.92	-1.2	PASS	ABNORMAL		
30	N		8	-0.44	-0.76	PASS	NORMAL		
31	N	PUL HAEMORRHAGE	4						APNEA ON DAY 1
32	N		2						
33	Y		4						
34	N		6						
35	N		4						STAGE III
36	Y	PNEUMONIA	40						ET ASPIRATE POSITIVE FOR KLEBSILLAE
37	N		3						
38	N	<1							
39	N		4						
40	N	THROMBOCYTOPENIA	7						
41	N	<2							
42	N	PNEUMONIA	21						ET ASPIRATE POSITIVE FOR KLEBSILLAE
43	N	THROMBOCYTOPENIA	3						
44	Y		5						
45	N	PNEUMOTHORAX	5						PNEUMOTHORAX ON ADMISSON/ ET DISPLACED DURING TRANSPORT
46	N	PUL HAEMORRHAGE	5						
47	N		5						
48	Y		6						
49	N	CELLUTIS,THROMBOCY	8						
50	Y		6						