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Therapeutic Hypothermia in Severe Neonatal Hypoxic-Ischemic Encephalopathy: A Case Report and Literature Review

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Abstract

Hypoxic-ischemic encephalopathy (HIE) remains a leading cause of neonatal mortality and long-term neurodevelopmental disability worldwide, with therapeutic hypothermia emerging as the standard neuroprotective intervention for eligible neonates with moderate to severe HIE. We report a case of a late preterm female neonate (36-37 weeks gestation) born via emergency cesarean section due to severe maternal preeclampsia with respiratory failure, who presented with severe birth asphyxia (APGAR scores 1/3), profound metabolic acidosis (umbilical cord pH 6.7, base excess -20 mmol/L), and severe encephalopathy (Thompson score 15). Therapeutic hypothermia was initiated within 6 hours of birth and continued for 72 hours, followed by controlled rewarming, with the patient requiring mechanical ventilation for 10 days and hospitalization for 17 days total. The patient demonstrated progressive neurological improvement with Thompson scores decreasing from 15 to 3 over the first four days of treatment, while cerebral regional oxygen saturation remained within normal limits throughout cooling therapy. The infant was successfully weaned from mechanical ventilation, achieved full enteral feeding, and was discharged home without apparent neurological sequelae. This case demonstrates the successful implementation of evidence-based therapeutic hypothermia protocols in severe HIE management, emphasizing that early recognition, appropriate patient selection, precise temperature control, and comprehensive supportive care are critical for optimal outcomes, while long-term neurodevelopmental follow-up remains essential for all HIE survivors.

Keywords— hypoxic-ischemic encephalopathy, therapeutic hypothermia, neonatal asphyxia

Abstrak

Ensefalopati hipoksik-iskemik (HIE) tetap menjadi penyebab utama kematian neonatal dan disabilitas perkembangan saraf jangka panjang di seluruh dunia, dengan hipotermia terapeutik muncul sebagai intervensi neuroprotektif standar untuk neonatus yang memenuhi syarat dengan HIE sedang hingga berat. Kami melaporkan kasus neonatus perempuan prematur akhir (usia kehamilan 36-37 minggu) yang lahir melalui operasi caesar darurat karena preeklampsia berat pada ibu dengan gagal napas, yang menunjukkan asfiksia berat saat lahir (skor APGAR 1/3), asidosis metabolik berat (pH tali pusat 6,7, kelebihan basa -20 mmol/L), dan ensefalopati berat (skor Thompson 15). Hipotermia terapeutik dimulai dalam 6 jam setelah kelahiran dan dilanjutkan selama 72 jam, diikuti dengan penghangatan kembali terkontrol, dengan pasien membutuhkan ventilasi mekanik selama 10 hari dan rawat inap selama total 17 hari. Pasien menunjukkan perbaikan neurologis progresif dengan skor Thompson menurun dari 15 menjadi 3 selama empat hari pertama pengobatan, sementara saturasi oksigen regional serebral tetap dalam batas normal selama terapi pendinginan. Bayi tersebut berhasil disapih dari ventilasi mekanik, mencapai pemberian makan enteral penuh,

dan dipulangkan ke rumah tanpa gejala sisa neurologis yang jelas. Kasus ini menunjukkan keberhasilan penerapan protokol hipotermia terapeutik berbasis bukti dalam penanganan HIE berat, menekankan bahwa pengenalan dini, pemilihan pasien yang tepat, kontrol suhu yang akurat, dan perawatan suportif komprehensif sangat penting untuk hasil yang optimal, sementara tindak lanjut perkembangan neurologis jangka panjang tetap penting bagi semua penyintas HIE.

Kata kunci*— ensefalopati hipoksik-iskemik, hipotermia terapeutik, asfiksia neonatal*

I. INTRODUCTION

Hypoxic-ischemic encephalopathy represents one of the most devastating neurological conditions affecting newborns worldwide, occurring in approximately 1.5 per 1,000 live births in developed countries. This condition results from inadequate oxygen delivery and reduced cerebral blood flow during the perinatal period, leading to complex pathophysiological cascades that can result in permanent neurological disability or death. Despite significant advances in obstetric and neonatal care over the past decades, HIE continues to be responsible for approximately 23% of all neonatal deaths globally, representing approximately 840,000 deaths annually.[1,2]

The introduction of therapeutic hypothermia as a neuroprotective intervention has fundamentally transformed HIE management, representing the first evidence-based treatment to demonstrate significant improvement in survival and neurodevelopmental outcomes. Multiple randomized controlled trials and subsequent meta-analyses have consistently demonstrated that cooling therapy reduces the combined outcome of death or major neurodevelopmental disability at 18-24 months by approximately 25%.[2]

The pathophysiology of HIE involves a complex cascade of cellular and molecular events that unfold in distinct phases following the initial hypoxic-ischemic insult. The primary injury phase results in immediate cellular energy failure due to impaired oxidative metabolism, leading to ATP depletion and failure of energy-dependent cellular processes. This initial phase is followed by a secondary energy failure phase that typically occurs 6-48 hours after the insult, characterized by oxidative stress, inflammation, excitotoxicity, and ultimately cell death. Therapeutic hypothermia specifically targets this secondary injury phase, explaining why early initiation within six hours of birth is crucial for optimal neuroprotective effects.[3,4]

We present a detailed case report of a late preterm infant who developed severe HIE following birth asphyxia in the context of maternal severe preeclampia. This case provides an opportunity to examine contemporary evidence-based management strategies, the critical role of therapeutic hypothermia in neuroprotection, and the importance of comprehensive supportive care in achieving optimal outcomes.

II. CASE PRESENTATION

PATIENT DEMOGRAPHICS AND BIRTH HISTORY

A female neonate was born at 36-37 weeks gestational age via emergency cesarean section at our tertiary care facility. The mother was a 37-year-old G3P1A1 who had received regular antenatal care from a midwife with obstetric consultation beginning in the seventh month of pregnancy. An ultrasound examination during this period revealed no fetal abnormalities and normal amniotic fluid volume; however, the mother was diagnosed with gestational hypertension at that time. The delivery was precipitated by severe preeclampsia complicated by acute respiratory failure and pulmonary edema, requiring maternal intubation and mechanical ventilation. The mother received multiple sedative agents including fentanyl, ketamine, and midazolam, while the cesarean section was performed under general anesthesia. Laboratory investigations revealed significant maternal leukocytosis (30,650/mm³) and anemia (hemoglobin 9.9 g/dL), while platelet count was elevated at 498,000/mm³. Both HIV and hepatitis B surface antigen tests were negative.

The infant's birth weight was 3,200 grams, body length 49 cm, placing her in the appropriate-for-gestational-age category according to Fenton growth curves. The

Ballard score confirmed gestational age at 36-37 weeks. However, the delivery circumstances resulted in severe birth asphyxia, evidenced by profoundly low APGAR scores of 1 at one minute and 3 at five minutes.

The infant presented with absence of spontaneous respiratory effort, weak muscle tone, and peripheral cyanosis. Immediate resuscitation efforts included positioning, drying, and tactile stimulation. Positive pressure ventilation was initiated with peak inspiratory pressure of 25 cmH_2O, positive end-expiratory pressure of 5 cmH_2O, and fraction of inspired oxygen at 30%. Initial heart rate was under 100 beats per minute and oxygen saturation remained critically low at 61% in the first minute. By the third minute, the infant remained apneic with inadequate respiratory effort, demonstrating nasal flaring and severe chest retractions, with oxygen saturation improving only to 63%. Endotracheal intubation was performed using a 3.5 mm endotracheal tube placed at 9 cm depth, followed by continued positive pressure ventilation with increased oxygen concentration to 50%. By the fifth minute, oxygen saturation reached 92%, chest expansion became adequate and symmetrical, peripheral cyanosis resolved, and chest retractions diminished significantly.

Laboratory and Diagnostic Findings

Blood gas analysis from umbilical cord blood revealed profound mixed respiratory and metabolic acidosis with pH 6.7, pCO_2 117 mmHg, pO_2 9 mmHg, bicarbonate 15.9 mmol/L, and base excess -20 mmol/L. Arterial blood gas analysis confirmed severe metabolic acidosis with pH 7.12, pCO_2 39 mmHg, pO_2 28 mmHg, bicarbonate 15.9 mmol/L, and base excess -21 mmol/L. Initial laboratory investigations revealed a complete blood count with hemoglobin 17.1 g/dL, hematocrit 48%, white blood cell count 20,210/mm^3, and platelet count 205,000/mm^3. Electrolyte panel showed sodium 138 mmol/L, potassium 3.6 mmol/L, and chloride 102 mmol/L. Renal function studies demonstrated blood urea nitrogen 28 mg/dL and creatinine 1.0 mg/dL. Random blood glucose was 95 mg/dL. Chest radiography performed on admission revealed bilateral lung field opacity consistent with neonatal pneumonia and possible respiratory distress syndrome, requiring ongoing respiratory support and antibiotic therapy.

The initial neurological examination revealed evidence of severe encephalopathy. The infant demonstrated hypotonia, lethargy progressing to coma, absent primitive reflexes including Moro and grasp reflexes, poor sucking reflex, and requirement for mechanical ventilation due to inadequate respiratory effort. The Thompson score, a validated assessment tool for HIE severity, was calculated at 15 points, indicating severe encephalopathy and meeting criteria for therapeutic hypothermia eligibility.[5] The Thompson score evaluation revealed maximum scores in multiple categories: tone (3 - flaccid), level of consciousness (3 - comatose), Moro reflex (2 - absent), grasp reflex (2 - absent), suck reflex (2 - absent), and respiration (3 - requiring mechanical ventilation). The fontanelle was not tense, and no seizures were observed during the initial assessment period.

Therapeutic Hypothermia Protocol Implementation

Based on the clinical presentation meeting established criteria for moderate to severe HIE, therapeutic hypothermia was initiated within 6 hours of birth[6]. The patient met multiple eligibility criteria including gestational age ≥36 weeks, evidence of perinatal hypoxia-ischemia (low APGAR scores, need for resuscitation, severe acidosis), and clinical evidence of severe encephalopathy (Thompson score >7).

Whole-body therapeutic hypothermia was implemented using passive controlled cooling method with continuous core

temperature monitoring via rectal probe. The target temperature range was maintained between 33°C and 34°C for a total duration of 72 hours[7]. Temperature was monitored continuously, and cooling was adjusted to maintain precise temperature control within the therapeutic range. During the cooling period, comprehensive monitoring included hourly vital sign assessment, continuous pulse oximetry, and cerebral regional oxygen saturation ($crSO_2$) monitoring using near-infrared spectroscopy (NIRS). The $crSO_2$ values remained within normal range (52-74%) throughout the cooling period, suggesting adequate cerebral perfusion during treatment.[8]

Clinical Course and Management

The patient required mechanical ventilation in pressure-controlled synchronized intermittent mandatory ventilation with volume guarantee (PC-SIMV + VG) mode. Initial ventilator settings included positive end-expiratory pressure of 6 cmH_2O, tidal volume of 12.8 mL (4 mL/kg), respiratory rate of 50 breaths per minute, and fraction of inspired oxygen of 40%. Oxygen saturation was maintained between 92-95% throughout the treatment period.

Fluid management during the cooling period included temporary fasting with total parenteral nutrition providing 60 mL/kg/day on day 1, progressively increasing to 80-100 mL/kg/day by days 2-3. The nutrition regimen included dextrose infusion at glucose infusion rate of 7.2 mg/kg/minute, protein at 2 g/kg/day, and lipid at 1 g/kg/day which will be increased gradually every day according to age. Antibiotic therapy was initiated empirically with ampicillin-sulbactam 100 mg/kg/day divided into two doses and gentamicin 5 mg/kg/dose administered every 36 hours, adjusted for gestational age. Metabolic acidosis was addressed with sodium bicarbonate correction to prevent rapid pH changes that could exacerbate neurological injury.

Rewarming and Recovery Phase

After completing 72 hours of therapeutic hypothermia, controlled rewarming was initiated at a rate of 0.5°C per hour to reach target normothermia of 36.5°C over approximately 7 hours[7]. During the rewarming phase, intensive monitoring continued with hourly vital signs, $crSO_2$ monitoring, neurological assessment, and blood glucose monitoring to detect any signs of clinical deterioration. The Thompson score showed progressive improvement over the treatment course, decreasing from the initial score of 15 to 6 on day 2, then to 3 on days 3 and 4, indicating significant neurological recovery. This improvement was reflected in enhanced muscle tone, improved level of consciousness, and gradual return of primitive reflexes.

By day 5, the patient was successfully weaned from mechanical ventilation and transitioned to continuous positive airway pressure (CPAP) with positive end-expiratory pressure of 6 cmH_2O and fraction of inspired oxygen of 30%. Enteral feeding was initiated with breast milk at 20 mL/kg/day via orogastric tube, with gradual advancement by 20-30 mL/kg/day while monitoring feeding tolerance.

Complications and Secondary Management

The clinical course was complicated by several issues requiring active management. Around day 10-12, the patient experienced respiratory deterioration requiring reinstitution of CPAP support, along with intermittent fever reaching 38.7°C and feeding intolerance manifested by vomiting 2-3 times daily. Laboratory investigations during this period revealed anemia with hemoglobin 9.8 g/dL, requiring careful monitoring but not transfusion. Blood cultures were obtained and remained negative for bacterial growth. Chest radiography showed persistent bilateral infiltrates consistent with evolving pneumonia. Antibiotic therapy was escalated

to second-line agents including cefoperazone-sulbactam 200 mg three times daily and amikacin 25 mg three times daily. Enteral feeding was temporarily reduced to 80-100 mL/kg/day to improve tolerance, with gradual re-advancement as tolerated.

The patient demonstrated gradual clinical improvement over the following days, with successful weaning from CPAP by day 13, resolution of fever, and improvement in feeding tolerance. By day 15, the patient was maintaining adequate oxygenation on room air and had achieved full enteral feeding at 150 mL/kg/day with good tolerance.

DISCHARGE AND FOLLOW-UP PLANNING

The patient was discharged home on the 17th day of hospitalization in stable condition. At discharge, the infant was breathing spontaneously on room air with oxygen saturations >95%, maintaining normal vital signs, and demonstrating age-appropriate neurological examination findings. Feeding was well established with breast milk at 150 mL/kg/day with normal sucking reflex and no signs of feeding difficulties.

Comprehensive discharge planning included detailed education for the family regarding signs and symptoms requiring immediate medical attention, proper feeding techniques, and importance of regular follow-up care. The family was instructed to monitor weight gain, feeding patterns, and developmental milestones at home. Follow-up arrangements included a scheduled visit to the neonatology outpatient clinic one week after discharge, with subsequent regular developmental assessments scheduled at 3, 6, 12, and 24 months of age to monitor for any signs of neurodevelopmental delay or other complications related to the HIE diagnosis.[9]

III. DISCUSSION

This case demonstrates the successful implementation of evidence-based therapeutic hypothermia protocols in the management of severe neonatal HIE. The patient presented with multiple high-risk factors including late preterm birth, severe maternal preeclampsia, profound birth asphyxia, and severe encephalopathy, all of which historically would have predicted poor outcomes in the pre-hypothermia era. The severe metabolic acidosis documented in this case (umbilical cord pH 6.7, base excess -20 mmol/L) provides objective evidence of significant tissue hypoxia and impaired cellular metabolism during the perinatal period[1]. These laboratory findings, combined with the clinical presentation of severe encephalopathy (Thompson score 15), indicate substantial disruption of normal cerebral energy metabolism and activation of secondary injury cascades.

The maternal complications, particularly severe preeclampsia with respiratory failure, created a complex clinical scenario affecting placental perfusion and fetal oxygenation. Preeclampsia is associated with placental insufficiency and altered uteroplacental blood flow, representing one of the most significant maternal risk factors for HIE development. The requirement for maternal intubation and high-dose sedation further complicated fetal well-being, although the clear amniotic fluid and absence of chorioamnionitis suggested that the primary pathophysiology was related to placental insufficiency rather than infectious complications[10]. The late preterm gestational age (36-37 weeks) represents an additional risk factor for HIE development, as these infants demonstrate increased vulnerability to hypoxic-ischemic injury compared to term infants due to incomplete brain maturation and reduced cerebral autoregulation capacity.[11]

The therapeutic hypothermia protocol implemented in this case adhered closely to established evidence-based guidelines[3]. The key elements of successful hypothermia management were demonstrated including appropriate patient selection, timely initiation within 6 hours of birth, precise temperature

control between 33-34°C, systematic monitoring during the 72-hour cooling period, and controlled rewarming at 0.5°C per hour[7].

The use of near-infrared spectroscopy for cerebral oximetry monitoring represents an important advancement in HIE management, providing real-time information about cerebral oxygenation that may not be apparent through conventional monitoring.[8] The normal $crSO_2$ values (52-74%) maintained throughout the cooling period suggest adequate cerebral perfusion during treatment, which correlates with the favorable neurological recovery observed in this case.

The progressive improvement in Thompson scores from 15 to 3 over the first four days provides objective evidence of neurological recovery and successful neuroprotection[5]. This degree of improvement is consistent with successful therapeutic hypothermia outcomes reported in clinical trials and suggests interruption of the secondary injury cascade that typically develops hours to days after the initial insult.

The complications encountered during this patient's course, including prolonged mechanical ventilation, development of pneumonia, and feeding intolerance, represent common challenges in HIE management that require careful attention to prevent secondary complications.[12] The respiratory complications may result from the primary neurological injury affecting respiratory drive, ventilator-associated lung injury, or secondary infections. The development of pneumonia around day 10, evidenced by fever, increased oxygen requirements, and radiographic changes, required prompt recognition and appropriate antibiotic escalation. The negative blood culture results suggest ventilator-associated pneumonia rather than bloodstream infection, highlighting the importance of infection prevention strategies in mechanically ventilated patients.

The feeding intolerance experienced around day 10-12 represents a common complication in HIE patients that may result from altered gastrointestinal motility related to autonomic nervous system dysfunction, medication effects, or intercurrent illness. The successful management of these complications without requiring blood product transfusion or other major interventions suggests appropriate monitoring and supportive care.

The short-term outcomes in this case appear favorable based on several positive indicators. The successful weaning from mechanical ventilation, establishment of full enteral feeding, absence of seizures, and improvement in neurological examination scores all suggest good early recovery from the acute injury.[9] The normal cerebral oxygen saturation values maintained during cooling therapy provide additional reassurance regarding cerebral perfusion adequacy. However, the assessment of long-term prognosis requires careful interpretation of available evidence. While therapeutic hypothermia reduces the incidence of severe disabilities such as cerebral palsy and intellectual disability, more subtle neurodevelopmental problems may still occur in a significant proportion of survivors.[13] Follow-up studies of children treated with therapeutic hypothermia have revealed that even those with apparently normal outcomes at 18-24 months may develop learning difficulties, attention problems, or behavioral issues that become apparent during school age.[14]

The absence of advanced neuroimaging studies in this case represents a limitation in comprehensive HIE assessment. Current guidelines recommend magnetic resonance imaging for all infants with HIE, preferably performed after completion of therapeutic hypothermia to optimize prognostic value. MRI findings, particularly involving the basal ganglia, thalamus, and posterior limb of the internal capsule, provide valuable

prognostic information that complements clinical assessment tools.[15,16]

Recent systematic reviews and meta-analyses continue to support therapeutic hypothermia as the standard of care for eligible neonates with moderate to severe HIE. A comprehensive meta-analysis has confirmed that therapeutic hypothermia significantly reduces the risk of death or major neurodevelopmental disability at 18-24 months.[13,17] The evidence demonstrates that cooling therapy reduces mortality by approximately 25% and major neurodevelopmental disability by approximately 23% in eligible patients. However, the interpretation of these outcomes requires recognition that even with therapeutic hypothermia, approximately 40-50% of infants with moderate to severe HIE will still experience death or major disability. This emphasizes the importance of continued research into adjunctive neuroprotective therapies and the critical need for comprehensive long-term follow-up and early intervention services for all HIE survivors.

IV. CONCLUSION

This case report demonstrates the successful implementation of evidence-based therapeutic hypothermia protocols in the management of severe neonatal HIE. The patient's favorable short-term outcomes, including neurological recovery and successful discharge without apparent sequelae, illustrate the potential benefits of timely recognition, appropriate patient selection, and comprehensive supportive care. Key factors contributing to the successful outcome include early recognition of HIE severity using validated assessment tools, prompt initiation of therapeutic hypothermia within the critical 6-hour window, precise temperature control throughout the 72-hour cooling period, comprehensive monitoring including cerebral oximetry, appropriate management of complications, and coordinated multidisciplinary care.

The case also highlights important challenges in HIE management, including the need for prolonged intensive care, management of complications such as pneumonia and feeding intolerance, and the importance of family education and support throughout the treatment process. While the short-term outcomes appear favorable, this case underscores the critical importance of long-term neurodevelopmental follow-up for all HIE survivors. Even infants with apparent good early recovery may develop subtle cognitive, behavioral, or learning difficulties that become apparent during childhood, emphasizing the need for ongoing surveillance and early intervention services.

Future directions in HIE management include investigation of adjunctive neuroprotective therapies, optimization of cooling protocols, development of improved prognostic biomarkers, and enhancement of long-term follow-up and intervention strategies. The continued refinement of evidence-based protocols and comprehensive care pathways will be essential for further improving outcomes for these vulnerable patients and their families. This case contributes to the growing body of evidence supporting therapeutic hypothermia as a life-saving intervention for neonatal HIE and demonstrates the importance of maintaining high standards of clinical care, family-centered approaches, and commitment to evidence-based practice in achieving optimal outcomes for these critically ill infants.

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