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The golden hour: providing very premature infants a favorable beginning

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Abstract

The first hour of life in a very premature neonate is a critical period of transition requiring extra-uterine adaptation of multiple organ systems for which the vulnerable neonate is ill prepared. Medical interventions provided to the neonate during this golden first hour of life can have significant implications on immediate survival and long term morbidities. Delayed cord clamping, delivery room temperature stabilization, strategies to establish functional residual capacity and gentle ventilation, early administration of dextrose and amino acid infusions, antibiotics when indicated and timely successful placement of peripheral or umbilical venous catheters are areas of focus during golden hour care. Premature infants born and resuscitated at tertiary and quaternary care centers have improved survival chances and outcomes when compared to similar "out-born" infants which highlight the role of experienced and skilled resuscitation teams in the golden hour. Strategies to standardize the various elements used in the resuscitation and stabilization of the very premature neonate that utilize quality improvement measures such as a golden hour protocol may help improve timeliness and efficacy of care provided in the first hour of life.

Keywords: very premature, golden hour, hypothermia, hypoglycemia, sepsis, surfactant, delayed cord clamping, parenteral nutrition

Abbreviations: IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; ELBW, extremely low birth weight; VLBW, very low birth weight; CPAP, continuous positive airway pressure; SI, sustained inflation; FRC, functional residual capacity; TPN, total parenteral nutrition

Introduction

Preterm birth is the greatest contributor of infant death and is also a leading cause of long term disabilities in children throughout the world. Infants born very preterm (<32 weeks) are at high risk of prematurity related mortality and morbidity.[1,2] The first hour of life is a critical period of transition requiring multiple adaptations to extra uterine life, for which the fragile preterm neonate is not prepared. Therefore, the vulnerable premature infant faces profound challenges in this transitional process that may adversely affect numerous short and long term outcomes and contribute to an increased risk of mortality and morbidities such as intraventricular hemorrhage (IVH), developmental delays, cerebral palsy and bronchopulmonary dysplasia (BPD).[3] The concept of care during the first hour of life in a premature infant parallels the concept of golden hour in trauma and emergency medicine where the first 60 minutes of definitive and critical care has a direct impact on patient outcome.[3,4] The golden hour strategy in neonatal medicine is an approach that reinforces effective communication and collaboration between multiple care providers using evidence based protocols and measures with a goal to deliver initial resuscitation and stabilization of a very premature infant in relatively short period of time.

There are numerous factors related to prematurity and the resultant underdeveloped organ systems that increase the complexity of stabilization following the birth of a very premature infant. The immature lung with underdeveloped alveoli, surfactant deficiency, immature nervous system with poor respiratory drive and weak compliant chest muscles which predisposes to alveolar collapse contribute to poor lung expansion and difficulty with gas exchange in these infants. Their extremely immature skin and lack of epidermal barrier promotes evaporative heat loss and higher body surface area-to-weight ratio and ineffective thermogenesis makes heat preservation in this population challenging, especially in the first precious hour of life. The detrimental effects of hypothermia may result in increased oxygen and metabolic demands, acid-base derangements, respiratory and circulatory compromise, hypoglycemia and even death.[1,5,6] Additionally, they have poor energy stores and are prone to develop metabolic derangements such as hypoglycemia due to failure in glycogen accretion. The preterm infants lack the cerebral defenses against hypoglycemia seen in term infants making them more prone to brain injury from these derangements.[7] On the flip side, early protein administration in this population helps prevent catabolism and buffer against hyperglycemia by initiating endogenous insulin production.[8] These neonates are also at an increased risk of serious blood stream infections due to their underdeveloped immune function. In addition, the presence of fragile germinal matrix blood vessels in the immature brain predisposes these infants to intracranial hemorrhage, the risk of which increases if there are lapses in the initial resuscitation and stabilization period. Many recent studies have reported improved outcomes for very preterm and very low birth weight (VLBW) babies born in tertiary neonatal intensive care units versus infants first born elsewhere and subsequently transferred to the tertiary NICU.[9-11] This suggests that presence of experienced neonatal resuscitation team and enhanced multidisciplinary approach during initial stabilization may significantly impact survival and outcomes in this population. The golden hour approach in neonatology thus relies not only on evidence based treatment and resuscitation protocols but also in team structure, communication and proficient work flow for prompt and skilled stabilization of this very vulnerable population within a critical time frame.

Discussion

The key areas of focus that require timely completion during the first golden hour of life of a very premature baby incorporates the following:

Delayed cord clamping

Delayed cord clamping in premature neonates is a simple procedure that the current evidence in medical literature seems to support for improving neonatal morbidity.[12] Systematic review of trials conclude that in uncomplicated premature deliveries delaying cord clamping for 30 secs to 3 minutes following delivery improves blood pressure, decreases IVH, lowers risk of necrotizing enterocolitis and need for blood transfusions or vasopressors.[13] However, long term benefits of this intervention and its impact on death or neuro-development are so far inconclusive. Also there is limited data on optimal timing of delayed cord clamping and potential benefits in non-vigorous or extremely premature periviable neonates. Cord milking has been suggested as an alternate and quick method of placental transfusion in deliveries which warrant immediate resuscitation in non-vigorous neonate.[14] Animal studies in preterm lambs demonstrate that onset of ventilation prior to umbilical cord clamping improves cardiac function by increasing pulmonary blood flow and also enhances cerebral and systemic oxygenation leading to a smoother extra-uterine cardiovascular adaptation.[15,16] Replicating such a setup to provide effective resuscitation and ventilation while still being attached to the placenta may be of immense benefit to a compromised premature neonate and is an area of further research.

Prevention of hypothermia

Heat loss usually exceeds heat production after birth. This is especially true in very premature neonates with minimal thermogenesis, a poorly developed skin barrier, exposure to multiple routes of heat loss (evaporative, conductive and convective) in the delivery room and increases in oxygen consumption putting them at increased risk of developing hypothermia if heat loss prevention measures are not initiated immediately after birth. For low birth weight infants, every 1 °C below 36 °C on admission temperature is associated with 28% increase in mortality risk.[17] Maintaining ambient temperature of the delivery room at 25-26 °C was shown to decrease cold stress in premature infants born at less than 32 weeks gestation.[18] Currently the standard practice during delivery and resuscitation of very premature neonates is not to dry the infant, but rather to place them in polyethylene bags or wraps and perform resuscitative measure within the plastic bag or occlusive skin wrapping. Additional heat loss is prevented by covering the head of the infant not covered by a plastic barrier with a hat. This minimizes evaporative heat loss and allows warming of infant from the radiant warmer.[19-21] The use of transwarmer or exothermic mattress have been studied in combination with plastic bags and hats and has successfully led to a reduction in incidence of hypothermia in premature infants less than 35 weeks gestational age.[22] There has been concern for inducing hyperthermia with such approach in some smaller studies and these infants need to be monitored closely.[23,24]

Respiratory stabilization

Very preterm neonates often have decreased alveolar compliance, a highly compliant chest walls, surfactant deficiencies, floppy airways and weak respiratory muscles. Hence, they are at increased risk for respiratory distress syndrome, pneumothorax and pulmonary interstitial emphysema in the short term and chronic lung disease and increased incidence of reactive airway disease in the long term. The goal of respiratory management is to provide adequate minute ventilation by improving lung compliance, avoiding apnea and decreasing work of breathing. During the initial resuscitation and first several minutes of life, oxygen supplementation is provided as required to keep oxygen saturations in the target range for age (1 min -60-65%, 2 mins - 65-70%, 3 mins - 70-75%, 4 mins - 80-85%, 5 mins -80-85% and 10 mins-85-95%).[25] Neonatal resuscitation program suggests starting FiO2 to be 21-30% and recommends against using high oxygen (FiO2 65% or greater) as it is a preference to avoid exposing preterm neonates to additional oxygen without data demonstrating a proven benefit for important outcomes.[25] The choice of an ideal initial respiratory modality in the delivery room remains elusive. Earlier studies focused on prophylactic administration of surfactant for very preterm neonates showed a decreased risk of air leak and neonatal mortality. However, in the era of greater utilization of maternal steroids and routine post-delivery stabilization on continuous positive airway pressure (CPAP) this view has been challenged.[26,27]

Appropriate application of post-delivery CPAP increases functional residual capacity, prevents alveolar collapse, improves compliance, increases airway diameter and splints the airway and diaphragm. The choice of CPAP vs prophylactic surfactant should be based on institutional experience, local practices and comfort with delivery room CPAP. While many techniques have been utilized to provide appropriate respiratory support to promote gentle ventilation and avoid iatrogenic injury due to volutrauma. Again, ventilation strategies selected should be based on institutional experience, local practices and comfort levels with certain modes of ventilation.

Sustained inflation (SI)

Adequate lung inflation is important for successful transition at birth. Most preterm neonates require assistance to aerate the lungs and establish functional residual capacity (FRC). CPAP and intermittent positive pressure ventilation are used as standard methods. In animal models, prolonged sustained inflations for 10-20s have been used alternatively to achieve FRC and lung aeration.[28] Clinical trials using SI at birth in neonates at birth showed decreased requirement for mechanical ventilation however decrease in BPD is not consistent.[29] Further studies to optimize the SI technique and address concerns of risk with pneumothorax are needed before this technique can be used routinely in practice.

CPAP

Immediate application of CPAP after preterm birth reduces the need for intubation, exogenous surfactant administration, and ventilator days, but does not change rates of BPD and/or death in this population. Appropriate application of post-delivery CPAP increases functional residual capacity, prevents alveolar collapse, improves compliance, increases airway diameter and splints the airway and diaphragm. Higher levels of CPAP (CPAP of 8 compared to CPAP of 5) resulted in increased risk of pneumothorax, so pressure needs to be delivered judiciously.[30,31] One may consider intubation and surfactant therapy (see below) to attenuate this risk. Both flow inflating bags and T-piece resuscitators can deliver CPAP in the delivery room, however self-inflating bags cannot deliver CPAP.

Intubation

Preterm neonates have highly compliant chest walls, surfactant deficiencies, floppy airways and weak respiratory muscles. Although many preterm neonates require positive pressure ventilation for stabilization, with appropriate post-delivery application of CPAP about half of the extremely low birth weight (ELBW) infants who are born can be managed without intubation or mechanical ventilation.[30] The subset of infants still showing signs of significant distress despite administration of non-invasive positive pressure may benefit from intubation and subsequent positive pressure ventilation. When requiring intubation, very preterm neonates may likely benefit for early administration of surfactant since severe distress is often tied to surfactant deficiency. At our institution, we deliver early surfactant in two aliquots, gently turning the infant on one side for one minute for the first aliquot then on their other side for minute for the subsequent aliquot. This is done while the infant remains in his/her plastic covering to allow for appropriate thermoregulation.

Early Initiation of Total Parenteral Nutrition (TPN)

Early administration of parenteral nutrition immediately after birth aims at minimizing postnatal deprivation of amino acids, glucose and nutrients as the prematurely born neonate is adapting to extrauterine life. The early initiation of parenteral amino acids is vital for prevention of protein catabolism and metabolic shock in the very low birth weight infants where the decline in essential amino acids in blood after disconnection from placenta triggers a starvation response leading to endogenous irrepressible glucose production and glucose intolerance. Early initiation of parenteral amino acids is also known to stimulate insulin secretion in the premature neonate in the absence of which insulin dependent pathways of transporter mediated glucose transfer may be affected leading to disruption of Na+ K+ ATP-ase activity and resultant intracellular energy failure and hyperkalemia[32] Hence providing parenteral nutrition in the first hour of life is an important goal of aggressive nutrition in prematurity and may promote better growth at 36 weeks postmenstrual age in extremely low birth weight infant population.[33,34] Successful early placement of peripheral vascular access or umbilical venous catheter and the delay in its radiologic placement confirmation may be barriers towards achieving early administration of parenteral nutrition. Many quality improvement studies have reported successful delivery of parenteral nutrition in first hour of life, prompt placement of umbilical venous and arterial catheters, timely completion of placement radiograph and faster acquisition of stock standard parenteral nutrition solution from pharmacy after implementation of a golden hour protocol.[6,35,36]

In our institution we administer 5% amino acid stock solution with 3 gram/kg/d protein infusion rate for all very an extremely premature infants in the first hour of life to deliver protein accretion similar to that of a reference fetus. The use of such standardized stock TPN with predetermined amounts of glucose and amino acid has increasingly become prevalent in neonatal care due to ease of availability, storage and focus on early initiation of TPN in this population.[37] Parenteral amino acid intake of 3-3.5 gram/kg/d in the first day of life has been shown to be both safe and effective in improving protein accretion in the very premature neonate[38,39] without any adverse clinical sequelae such as metabolic acidosis or hyperammonemia.[40] Recently, there have been some concerns about electrolyte derangements such as hypokalemia, hypophosphatemia and hypercalcemia in growth restricted extremely low birth weight premature infants who were exposed to such standardized high amino acid parenteral nutrition in first days of life.[41,42] Whether an individualized parenteral nutrition approach is more appropriate in such population starting on the first day of life needs further examination.

Prevention of hypoglycemia

Early transient hypoglycemia is a frequent occurrence in premature neonates shortly after birth. VLBW infants are at higher risk of neonatal hypoglycemia secondary to restricted reserve of glycogen and fat which are typically accreted in the third trimester of pregnancy.[43] Although there is no consensus on what level and duration of hypoglycemia is detrimental, recurrents periods of hypoglycemia have been shown to result in lower head circumferences and neuro developmental deficits in small-for age- premature infants.[44] Early initiation of dextrose infusion is critical during the first hour of life to prevent hypoglycemia induced cerebral energy failure and prevent possible damage as well as ensure a smooth extrauterine adaptation for very premature infants. In a study of VLBW infants, initiation of glucose intravenous infusion within thirty minutes of birth was recommended as best practice.[36] In our institution, we initiate parenteral nutrition in very premature neonates with 10% dextrose in combination with 5% amino acid stock solution in the first hour of life aiming for glucose delivery of 5-6 mg/kg/min.

Early initiation of antibiotics

Serious blood stream infections and early onset sepsis are important causes of morbidity and mortality in premature infants. Several studies on early onset sepsis in neonates have emphasized initiation of antibiotics in the first hour of life when sepsis is clinically suspected to prevent serious sequelae.[45-47] Challenges in establishing intravenous access or central venous catheter in a very premature neonate may impact adversely the time to initiation of antibiotics. Application of golden hour quality improvement initiatives, having dedicated personnel for placement of vascular access and better communication and collaboration with pharmacy can lead to improvement in antibiotic initiation time in the first sixty minutes of life.[9]

The success of any golden hour protocol for premature neonate begins with a highly skilled and effective team in the delivery room and includes a standard road map guiding workflow during the resuscitation and the stabilization process that starts in the delivery room and continues in the NICU. The road map and workflow should focus on the key areas of safe and timely interventions aimed at improving outcomes and subsequent completion of the admission process to the neonatal intensive care unit in the first sixty minutes of life. In Table 1, we briefly outline five quality improvement projects that were reported and presented at national meetings in recent years to improve the timeliness and quality of interventions on premature infant during the golden hour of life and the outcomes that were achieved.

Table 1 Quality improvement projects centered on improving golden hour care in premature neonates

Study and Year	Study Design	Study Population	Significant Outcomes
Ashmeade et al.[35]	Quality Improvement: Golden hour Pathway (GHP)	ELBW (N=295, 173 infants pre GHP and 173 in Post GHP Cohort)	1. Improved Birth to Surfactant Administration Time 2. Improved Admission Body Temperature 3. Sooner Administration of TPN
Lambeth et al.[48]	Quality Improvement: Golden Hour	(N=205, 50 Infants Pre-Protocol and 105 Infants Post-Protocol) VLBW	1. Sooner Administration of TPN 2. Sooner Administration of Antibiotics
Bhandary et al.[49]	Quality Improvement: Golden Hour	ELBW	1. Sooner Successful Placement and Verification af Umbilical Catheter 2. Decrease in Severe Grade IVH

Table Continued...

Study and Year	Study Design	Study Population	Significant Outcomes
Reuter et al.[50]	Quality Improvement: Golden Hour	ELBW	1. Faster Placement of Umbilical Satheter 2. Decrease in IVH (All Grades)
Castrodale et al.[6]	Quality Improvement : Golden Hour	Extremely Premature Infants Born ≤ 28 Weeks Gestation (N=225, 106 Infants in Pre-Protocol and 119 Infants in Post Protocol Group	1. Higher admission body temperature and avoidance of hypothermia 2. Higher admission blood glucose level in euglycemic range 3. Faster initiation of TPN via peripheral intravenous catheter or umbilical catheter

Abbreviations: ELBW, extremely low birth weight; VLBWL, very low birth weight; GHP, golden hour pathway; IVH, intraventricular hemorrhage; TPN, total parenteral nutrition

These projects demonstrate that adoption of a standardized interdisciplinary team approach in the delivery room and NICU to care for the very premature infant in the first golden hour of life can be advantageous in delivering more efficient and timely care to the vulnerable neonate.

Conclusion

An increasing body of evidence substantiates that medical interventions done during resuscitation and stabilization of a very premature infant may have a direct impact on immediate survival and long term morbidities. A multitude of complex decisions and tasks need to be completed in a brief time period following birth of a very premature infant to provide the best chances for a smooth transition to postnatal life and ensure positive outcomes. A standardized evidence based approach of team development, effective communication and enhanced performance by utilization of a 'golden hour for neonate' protocol by interdisciplinary teams caring for high risk newborns may improve timeliness of interventions and advance outcomes.

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Conflicts of Interset

None.

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