Editorial

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Evidence-Based Neonatal Care

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Abstract:

Aging societies are developing around the world while the number of newborns is decreasing. The best neonatal care is a crucial issue since prematurity is surging along with high mortality and morbidity in developing countries. However, the basic areas of evidence-based practice in neonatal care still have limited information because both the short- and long-term outcomes of this fragile population need to be considered. Sophisticated neonatal care is a new topic for improvement of survival and long-term neurodevelopmental outcomes. Randomized controlled trials and meta-analyses in neonatal care were reviewed and the local epidemiology was integrated to implement evidence-based neonatal care.

Keywords: evidence-based practice, neonatal intensive care unit, newborn, perinatal care

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Introduction

Knowledge of neonatal practice is rapid growing in evidence-based medicine. Many clinical trials were done to determine the best neonatal care available and decrease the mortality and morbidities, especially in prematurity.[1,2] Preterm neonates present vast and challenging problems for clinicians, pediatricians, and neonatal nurses.[2] We reviewed clinical trials from randomized controlled trials and meta-analyses that included neurologic, respiratory, cardiovascular, gastrointestinal tract disorders, and sepsis in neonates.

Neurologic disorders

Neonatal survivals have improved around the world, especially in very low birth weight infants (VLBW, birth weight less than 1,500 grams); however, neuro-developmental outcomes are challenging for neonatal teams. Neuroprotective benefits in prematurity and asphyxia are a hope for the parents and clinicians.

Antenatal magnesium sulphate ($MgSO_4$) for fetal neuroprotection can be given close to the planned or expected preterm birth to reduce the burden of death and cerebral palsy (CP) in very preterm infants. The loading dose of $MgSO_4$ in the clinical trials was 4 grams with or without a 1-2 gram(s)/hour as the maintenance dose. There was a significant reduction in the risk of death or CP with $MgSO_4$ treatment in preterm births (<37 weeks' gestation) compared with no treatment [relative risk (95% confidence interval), RR (95% CI) 0.86 (0.75, 0.99)]. Moreover, a strong protective effect from $MgSO_4$ treatment was found in CP survivors [RR (95% CI) 0.68 (0.53, 0.87)][3] and in moderate to severe CP babies who were almost <34 weeks' gestation the protective effect was from 2.1% to 1.3% [RR (95% CI) 0.61 (0.42, 0.89)].[4] The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine support the short-term use of magnesium sulfate in fetal neuroprotection before anti-cipated early preterm (less than 32 weeks of gestation) delivery.[5] Routine practice should be considered from the aspects of benefit or incidence of outcome. If the incidence of moderate to severe CP in your hospital is less than 1.3%, routine prophylaxis in a fetus who is less than 34 weeks may not be needed. Early prophylactic therapy using recombinant human erythropoietin (rhEPO) in preterm infants after birth (almost less than 32 weeks' gestation within the first 48–96 hours and applied in lower doses 1,200–1,750 IU/kg per week) reduced the incidence of children with Mental Developmental Index (MDI)<70 from 15.7% to 8.4% at 18 to 24 months of corrected age [RR (95% CI) 0.51 (0.31, 0.81)].[6] Besides antenatal $MgSO_4$ and neonatal rhEPO, "prophylactic antibiotics with intact membranes" or "repeat doses compared with a single course of antenatal corticosteroids" for women at risk of preterm labor do not clearly impact fetal neuroprotection.[7]

Therapeutic hypothermia (core temperature 33-34 °C within 6-hour postnatal age for 72 hours followed by re-warming at 0.5 °C per hour) for ≥35 weeks' gestation neonates with evidence of intrapartum asphyxia and moderate to severe encephalopathy reduced the mortality or major neurodevelopmental disability at 18 months of age by 61.4% to 46.0% [RR (95% CI) 0.75 (0.68, 0.83)] but there were significant statistical differences of adverse effects that increased sinus bradycardia and thrombocytopenia in the hypothermia group.[8] However, cooling to lower than 33.5 °C or cooling for longer than 72 hours initiated at 6 to 24 hours after birth did not decrease death or moderate to severe disability at 18 months of age.[9,10] The long-term outcome of patients who survived total body hypothermia at 6 to 7 years of age had an intelligence quotient score of ≥85 or more [RR (95% CI) 1.31 (1.01, 1.71)] from 39.4% to 51.7%.[11] The use of adjunct therapies, that include xenon, darbepoetin, erythropoietin, topiramate, levetiracetam, phenobarbital, N-acetylcysteine or melatonin, needs more new clinical trials for moderate to severe encephalopathy.

In conclusion, antenatal $MgSO_4$ and neonatal rhEPO are the neuroprotections in the preterm fetus and neonate as well as moderate to severe CP (<34 weeks) and neurocognitive outcome (<32 weeks), respectively. Therapeutic hypothermia (≥35 weeks) prevented death and neurocognitive outcomes in both the short- and long-term studies.

Respiratory disorders

Respiratory distress is the most common problem in the neonatal intensive care unit (NICU) which includes bronchopulmonary dysplasia (BPD), apnea of prematurity, and use of non-invasive ventilation (NIV). Prevention of long-term respiratory complications reduces mortality, home therapy, length of stay, and hospital cost.

Systemic postnatal corticosteroids prevented BPD in preterm infants (<37 weeks) but we should be aware of the incidence of CP if corticosteroids are commenced within the first seven days of life.[12,13] Inhaled postnatal corticosteroids prevented BPD among survivors in VLBW infants particularly in patients who began during the first two weeks after birth[14] but there was no significant difference if started after the first week of life.[15] Nonetheless, there is no evidence that inhaled corticosteroids are better than systemic corticosteroids for ventilator-dependent preterm infants.[16]

Methylxanthine therapy reduced apnea and the use of intermittent positive pressure ventilation (IPPV) in the first two to seven days in preterm infants with recurrent apnea.[17] Caffeine prevented postoperative apnea and bradycardia and episodes of oxygen desaturation in growing preterm infants who underwent general anesthesia for surgery.[18] Methylxanthines increased the chances of successful extubation of preterm infants within one week of age.[19] The results of this review did not support the use of prophylactic caffeine for preterm infants at risk of apnea.[20]

In the Caffeine for Apnea of Prematurity (CAP) trial, caffeine citrate (20 mg/kg for loading then 5-10 mg/kg for maintenance, dose of caffeine base=half dose of caffeine citrate) therapy for apnea of prematurity reduced the rates of bronchopulmonary dysplasia[21], and improved the rate of survival without neurodevelopmental disability [cerebral palsy and cognitive delay (MDI<85)] at 18 months.[22] Neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children with VLBWs who were assessed at 5 years.[23] Caffeine therapy for apnea of prematurity did not significantly reduce the combined rate of academic, motor or behavioral impairments but was associated with a reduced risk of motor impairment in 11-year-old children with VLBW.[24] Neonatal caffeine therapy for apnea of prematurity improved the visuomotor, visuoperceptual and visuospatial abilities at the age of 11 years.[25]

NIV modalities, which included nasal continuous positive airway pressure (nCPAP), nasal biphasic positive airway pressure (nBiPAP), and nasal IPPV (nIPPV), prevented reintubation in the NICU. A recent meta-analysis reported that the nIPPV and nBiPAP modes demonstrated superiority to nCPAP in preventing extubation failure in preterm neonates.[26] Nasal high frequency oscillation (nHFO) is a relatively new mode of NIV in neonates.[27,28] nHFO is the application of a bias flow that generates a continuous distending positive pressure with superimposed oscillations which have a constant frequency and an active expiratory phase. The nHFO mode mixes and matches together the benefits of HFO [no need for synchronization and high carbon dioxide (CO_2) clearance] and nCPAP (increase in functional residual capacity to improve oxygenation).[29,30] Heated humidified high-flow nasal cannula (HHHFNC) are increasingly being used as a form of NIV for preterm infants. HHHFNC has similar rates of efficacy to other forms of NIV in preterm infants for preventing treatment failure, BPD and death. However,

most evidence is available for the HHHHFNC use as post-extubation support. However, further research is needed to study the different modes of NIV for the prevention of extubation failure.

In conclusion, systemic corticosteroids after 1 week and inhaled corticosteroids during the first two weeks can prevent BPD in preterm infants. Methylxanthine therapy reduces apnea, use of IPPV ventilation, and short- and long-term neurodevelopmental disability. Nasal IPPV and BiPAP are more effective in preventing extubation failure compared to nCPAP.

Cardiovascular disorders

Patent ductus arteriosus (PDA) increases the risk of BPD, necrotizing enterocolitis (NEC) or the need for surgical ligation. Indomethacin therapy is the standard treatment for medical ligation of PDA. Ibuprofen and paracetamol therapies are the alternative treatments for PDA. There were no significant differences between paracetamol and either ibuprofen or indomethacin in the failure to close a PDA in preterm or low birth weight infants. However, gastrointestinal bleeding was lower in the paracetamol group versus the ibuprofen group [RR (95% CI) 0.28 (0.12, 0.69)]. The serum levels of creatinine were lower in the paracetamol group compared with either the ibuprofen or indomethacin group. Platelet counts and daily urine output were higher in the paracetamol group compared with either the ibuprofen or indomethacin group.[31] Therefore, paracetamol is an alternative treatment if a neonate has a bleeding tendency or renal insufficiency. However, long-term neurodevelopmental outcomes should be a concern following prenatal and postnatal exposure to paracetamol which needs more trials.

Gastrointestinal tract disorders

Human milk feeding, prebiotics, prebiotics, synbiotics (probiotics and prebiotics), and lactoferrin make a balance in the intestinal microbiome and prevent NEC.[32-34] Evidence-based medicine, synbiotics, and probiotics can decreased NEC but not prebiotics alone.[35] Probiotics decreased the incidence of "all-cause mortality"[36-39], "NEC stage II or greater", and "late-onset sepsis"[40] in preterm neonates. Strain-specific sub-meta-analyses showed a significant effect of probiotic mixtures and bifidobacteria on NEC.[37] However, large and recent randomized controlled trials found no differences in the incidence of death, NEC, sepsis, or growth in preterm neonates who were given probiotics (*Bifidobacterium lactis* or *B. longum* or both[41] or *B. breve*[42]) compared to placebo. Enteral lactoferrin supplementation, with or without probiotics, decreased "late-onset sepsis" and "NEC stage II or III" in preterm infants without adverse effects.[43]

Sepsis

Chorioamnionitis or intra-amniotic infection is associated with significant maternal, perinatal, and long-term adverse outcomes. "Intrauterine inflammation or infection or both" can be abbreviated as "Triple I"[44,45] and used instead of chorioamnionitis. The definition and treatment of clinical chorioamnionitis and suspected Triple I following new evidence are given in Table 1.[44,45]

Administration of intravenous immunoglobulin (IVIG) for prophylaxis showed a significant reduction in sepsis [RR (95% CI) 0.85 (0.74, 0.98)] from 17.2% to 14.5% in preterm and/or low birth weight infants.[46] However, there were no statistically significant differences in mortality from infection for either prophylaxis or treatment with IVIG administration.[46,47] Moreover, IgM-enriched IVIG did not significantly reduce mortality during hospital stay in infants with suspected infection. Routine administration of IVIG or IgM-enriched IVIG to prevent mortality in infants with suspected or proven neonatal infection is not recommended.[47]

Table 1 Comparison of definition and treatment in healthy-appearing or asymptomatic neonates between clinical chorioamnionitis and suspected Triple I

Scope	Clinical chorioamnionitis	Suspected Triple I
Definition	1. Presence of maternal fever of greater than 38 °C and 2. At least 2 of the following criteria: 2.1 Maternal leukocytosis (greater than 15,000 cells/mm^3) 2.2 Maternal tachycardia (greater than 100 beats/minute) 2.3 Fetal tachycardia (greater than 160 beats/minute) 2.4 Uterine tenderness 2.5 Foul odor of the amniotic fluid	1. Maternal oral temperature 39.0 °C or greater on any one occasion without a clear source (if the oral temperature is 38.0-39.0 °C, repeat the measurement in 30 minutes; if the repeat value remains at least 38.0 °C, it is documented fever) 2. Any of the following: 2.1 Baseline fetal tachycardia (greater than 160 beats per min for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability) 2.2 Maternal white blood cell count greater than 15,000 per mm^3 in the absence of corticosteroids 2.3 Definite purulent fluid from the cervical os
Treatment	-require antimicrobial agents soon after birth and independent on gestational age and results of initial complete blood count and C-reactive protein	-Gestational age less than 35 weeks: work-up (complete blood count and C-reactive protein) and empirical antimicrobial prophylaxis -Gestational age 35 weeks or greater: observe and re-evaluation (close monitor within 6 hours until observe 48 hours of life)

Prophylactic oral/topical non-absorbed antifungal agents [RR (95% CI) 0.20 (0.14, 0.27)][48] and prophylactic systemic antifungal agents [RR (95% CI) 0.43 (0.31, 0.59)][49] found a statistically significant reductions in the incidence of invasive fungal infection (IFI) in VLBW infants from 31.1% to 3.8% and 12.9% to 6.3%, respectively. However, the incidence of IFI was very high in the control groups. The incidence of IFI in VLBW infants at Songklanagarind Hospital was 2.0% which was lower than the intervention group. Therefore, the routine prophylaxis of both administrations needs an understanding of the local epidemiology.

In conclusion, neonatal sepsis should be considered differently between clinical trial efficacy and real-world effectiveness including the local epidemiology.

Conclusion

Evidence-based practice is imperative care to improve the outcomes. Besides reduced mortality, long-term morbidities or neurodevelopmental outcomes should be the concerns for the best quality of life. Better outcomes in preterm infants have a high cost-effectiveness for long life.

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