Neuroprotección Perinatal para Infantes Extremadamente Pretérmino

Alexis S. Davis, MD, MS Epi[1] Victoria K. Berger, MD[2] Valerie Y. Chock, MD, MS Epi[1]
1 Division of Neonatal-Developmental Medicine, Stanford University,
Palo Alto, California
2 Division of Maternal-Fetal Medicine, University of California, San
Francisco, San Francisco, California
Am J Perinatol 2016;33:290–296.

El cerebro prematuro es vulnerable a la injuria a través de múltiples mecanismos a partir de injuria cerebral directa por isquemia y hemorragia, injuria indirecta por medio de procesos inflamatorios, y aberraciones en el crecimiento y desarrollo. Mientras que la prevención del nacimiento pretérmino es la mejor estrategia neuroprotectora, esto no siempre es posible. Este artículo revisará varias prácticas obstétricas y neonatales que han mostrado tener un efecto neuroprotector sobre el cerebro en desarrollo.
Palabras clave
► muy bajo peso de nacimiento
► injuria cerebral
► neuroprotección
► resultados
► infante prematuro

Pese a las mejoras en la tasa de nacimientos prematuros en los últimos años, la proporción de infantes de muy bajo peso de nacimiento (MBPN) permaneció estable en 2013 en Estados Unidos en 1.4% de los nacidos vivos (1)En números absolutos, esto se traduce en aproximadamente 55.000 niños nacidos con riesgo de injuria neurológica cada año. Los factores de riesgo para resultado adverso en el neurodesarrollo en esta población vulnerable incluyen injuria neurológica directa como ser hemorragia intraventricular e intraparenquimatosa (2, 3) y daño indirecto resultante de inflamación o infección. (4, 5) Hasta el 30% de los niños MBPN con neuroimágenes normales pueden estar en riesgo de resultados adversos,(6) sugiriendo un rol para insulto a nivel celular con alteraciones en el crecimiento (7) y la conectividad(8) en el cerebro en desarrollo.

Los primeros intentos de mejorar el resultado neurológico en niños pretérmino estaban dirigidos a prevenir la injuria reduciendo la tasa de hemorragia intraventricular (HIV).Mientras que los efectos iniciales del fenobarbital antenatal y la profilaxis con indometacina parecieron favorables en el período neonatal, no tuvieron un impacto significativo n los subsiguientes resultados en el neurodesarrollo. (9, 10) La prevención del nacimiento prematuro y la extensión de la gestación por medio de la progesterona antenatal, el cerclaje profiláctico, y la aplicación juiciosa de la tecnología reproductiva artificial es la última estrategia para reducir las tasas de infantes sobreviviendo con secuelas neurológicas. (11) Si el nacimiento prematuro no puede ser prevenido, sin embargo, existen varias intervenciones para reducir el riesgo de resultados adversos en niños extremadamente prematuros. Esta revisión describirá las estrategias en el período anteparto, durante la resucitación y transición a la vida extrauterina, y las terapias postnatales para reducir el riesgo de resultado adverso. (Tabla 1)

Estrategias Antenatales para Neuroprotección

Corticosteroides Antenatales

El empleo de corticoides antenatales (CAN) frente a una sospecha de parto prematuro fue descripto por primera vez en 1972 por Liggins y Howie, que demostraron la efectividad de los coroticosteroides para reducir el síndrome de distress respiratorio y la HIV entre bebés prematuros. (12) Siguiendo a la introducción de CAN, más estudios surgieron mostrando los mismos resultados favorables. (13, 14) La revisión Cochrane mostró una reducción significativa en aquellos que recibieron CAN previo al nacimiento prematuro. (15) Debido al importante rol de CAN, el Instituto Nacional de Salud (NIH) publicó un consenso en 1995 recomendando ofrecer CAN a los pacientes en riesgo de parto entre las 24 y 34 semanas. (16) Un estudio más reciente que evaluó la evolución de los niños prematuros extremos nacidos antes de las 29 semanas concluyó que la HIV era menos común entre aquellos que recibieron CAN. (17) La administración de CAN a mujeres en riesgo de parto prematuro es considerada la intervención más beneficiosa disponible para los obstetras para reducir la morbilidad neonatal respiratoria y neurológica (18)

Pese a que los beneficios a corto plazo de la administración de CAN ha sido ampliamente valorada, los efectos sobre el neurodesarrollo a largo plazo han sido cuestionados, y los estudios han mostrado resultados variables. La Neonatal Research Network ha informado tasas más bajas de muerte o déficit de neurodesarrollo a los 18-22 meses de edad corregida, incluyendo mejoras significativas en la tasa de muerte, HIV, y leucomalacia periventricular. (19) En un seguimiento a 30 años del trabajo de esteroides de Auckland, no hubo diferencia en los resultados cognitivos entre los niños expuestos a CAN y aquellos expuestos a placebo, (20) y esto fue verificado en un meta-análisis Cochrane. (15) Sin embargo, un meta-análisis más reciente que incluyó 14 estudios sobre los efectos a largo plazo en el neurodesarrollo de CAN, mostró un resultado favorable, con reducción de parálisis cerebral entre niños nacidos antes de las 34 semanas. (21) Más importante, se demostró una disminución del riesgo de severa discapacidad en los infantes más prematuros, con 34% de prevalencia de discapacidad severa en el grupo expuesto a esteroides comparado con 44% en aquellos no tratados. (21)

Dada la disminución de riesgo documentada de morbilidad respiratoria y neurológica cuando se administran CAN, las guías de prácticas actuales recomiendan un curso de CAN cuando se sospecha nacimiento prematuro, con 2 inyecciones de 12 mg de betametasona intramuscular separadas por 24 horas o 4 inyecciones intramusculares de 6 mg de dexametasona administradas cada 12 horas. (18) Está surgiendo evidencia que sugiere considerar aplicar un curso de rescate si la madre, que originalmente recibió CAN pero no tuvo el parto, vuelve a tener riesgo de parto antes de las 34 semanas. (18, 22) Repetir las dosis después de un curso de rescate no está recomendado, ya que dosis repetidas han sido asociadas a detención del crecimiento fetal y de la circunferencia craneana. (23, 24)

Sulfato de Magnesio

La asociación entre el sulfato de magnesio y mejor resultado neurológico se reconoció por primera vez en estudios de infantes de madres pre-eclámpticas expuestas a sulfato de magnesio demostrando tasas más bajas de HIV y parálisis cerebral (PC). (25-27) En 2003, un estudio mostró una tendencia no significativa hacia tasas en descenso de PC con la exposición al sulfato de magnesio en niños nacidos antes de las 30 semanas. (28) Más recientemente, un estudio de infantes nacidos entre las semanas 24 a 31 demostró una significativa reducción en la tasa de PC para niños expuestos a sulfato de magnesio (1.9 vs. 3.5%). (29) Una revisión Cochrane publicada en el 2009 concluyó que pese a no haber descenso en la mortalidad, había una reducción en PC y disfunción motora gruesa entre los niños expuestos a sulfato de magnesio, con un número de madres necesarios a tratar de 63. (30) No se conoce el mecanismo preciso por el cual el sulfato de magnesio ejerce un beneficio neuroprotector, pero se especula que posee efectos anti-inflamatorio y anti-excitotóxico mientras que también mejora el flujo sanguíneo cerebral y

estabiliza las fluctuaciones de la presión sanguínea en el recién nacido reduciendo la demanda metabólica cerebral. En respuesta a la creciente evidencia demostrando reducción de las tasas de PC, el American College of Obstetricians and Gynecologists (ACOG) con la Sociedad de Medicina Materno Fetal publicaron un consenso apoyando el empleo de sulfato de magnesio para neuroprotección en mujeres en riesgo de dar a luz antes de las 32 semanas de gestación. (33)

Manejo en Sala de Partos y Cuidado durante la transición a la vida postnatal

Las estrategias específicas en sala de partos para preservar el neurodesarrollo a largo plazo del niño pretérmino quedan como meta importante. Varias áreas de investigación actual incluyen la saturación ideal de oxígeno en los primeros minutos de vida, enfoques óptimos de ventilación y presiones iniciales de distensión pulmonar, prácticas para evitar de la mejor forma la hipotermia, y esfuerzos para minimizar la necesidad de compresiones cardíacas y resucitación extensa. (34) No enfocaremos en intervenciones específicas de la sala de partos, ya que será expuesto en otro artículo de estas series, además de exponer la práctica de clampeo tardío del cordón como corresponde a niños prematuros.

Clampeo tardío del cordón

El clampeo tardió del cordón (CTC) también conocido como clampeo programado del cordón umbilical o transfusión placentaria, ha experimentado varias etapas de interés en investigación y cambios de definición. (35) En la era pre-moderna de la medicina, el clampeo "temprano" del cordón fue definido como el realizado aproximadamente al minuto de vida, y clampeo demorado al producido a los 5 minutos o posterior. Definiciones modernas operacionales parecen igualar clampeo temprano con inmediato, en los primeros 15 segundos de vida; el momento del CTC varía según los estudios, entre 30 segundos hasta 1 y 5 minutos de vida. En los 1960 y 70, el CTC demostró reducir la incidencia de SDR en niños pretérmino, una observación inicialmente observada por veterinarios como el "Sindrome Barker Foal" y trasladado a otros modelos animales. El CTC perdió terreno en la era postsurfactante, en que el énfasis del cuidado de los niños extremadamente pretérmino se orientó hacia iniciar los esfuerzos de resucitación tan pronto como fuera posible y por la preocupación acerca de hiperbilirrubinemia e hiperviscosidad en aquellos expuestos a CTC.

Hemos cerrado el círculo, y el interés en el CTC se ha renovado con múltiples trabajos clínicos en infantes pretérmino orientados a la prevención de la anemia de la prematurez. Una revisión Cochrane en 2004 revisó 7 estudios conducidos mayormente en los 80 y 90 y afirmó el beneficio del CTC en niños de menos de 37 semanas reduciendo la necesidad de transfusiones de glóbulos rojos, mejorando la presión sanguínea, y disminuyendo la tasa de HIV. (36) Más trabajos y meta-análisis han confirmado los beneficios hematológicos y fisiológicos del CTC, generalmente sin efectos adversos tales como bajo score de Apgar, acidosis, o hipotermia. (37-40) Se especula que el CTC puede conferir beneficios adicionales inmunológicos y regenerativos a través de la transferencia de células madre para mejorar varias morbilidades neonatales así como enfermedades relacionadas a la edad. (41) Debido al creciente cuerpo de literatura, la ACOG publicó una opinión de Comité en 2012 que recomendó el CTC hasta 60 segundos para niños pretérmino pero notó que había áreas que requerían investigación adicional incluyendo la programación óptima según el tipo de parto (vaginal vs. Cesárea) y riesgos y beneficios conferidos a los niños más prematuros (definidos como <28 semanas EG). (42)

Los reportes acerca de los beneficios a largo plazo del CTC son escasos y deben aún demostrar si existe beneficio significativo sobre el neurodesarrollo. (39) Sin embargo, un estudio acerca de

los resultados a los 4 años sobre CTC en una población de niños de término, de bajo riesgo, demostró mejoras en las áreas motora fina y social, particularmente en niños. (43) El CTC es más efectivo cuando ya se ha instalado la respiración, permitiendo así que el lecho vascular pulmonar se llene con sangre. (44) Variables adicionales para optimizar la transfusión placentaria incluyen la posición del bebé con respecto a la placenta para permitir un óptimo flujo por gravedad y la presencia de contracciones uterinas, incluyendo la administración de oxitocina. (45) Las áreas actuales de investigación incluyen 1) la expresión del cordón umbilical tanto para facilitar la transfusión placentaria o cuando es necesario iniciar resucitación antes de que se produzca el CTC, (46, 47) y 2) el desarrollo de carros de resucitación móviles para iniciar resucitación y proveer soporte respiratorio antes del clampeo del cordón umbilical. (48) Más aún, son necesarios datos adicionales acerca de los resultados a largo plazo que avalen o refuten los beneficios del CTC.

Prácticas de Resucitación y Neuromonitoreo después del nacimiento

El monitoreo cerebral en sala de partos con NIRS puede ayudar a guiar la resucitación para mejorar los resultados del neurodesarrollo.NIRS es un método no invasivo para monitorear continuamente la oxigenación del tejido cerebral y puede fácilmente ser aplicado a los infantes pretérmino durante la reanimación en los primeros minutos de vida. (49 Los infantes pretérmino que requieren soporte respiratorio en sala de partos han mostrado tener niveles más bajos de oxigenación del tejido cerebral que aquellos que no requieren intervención. (50) Más aún, la resucitación ventilatoria efectiva después del nacimiento en niños pretérmino resulta primero en aumento de la oxigenación del tejido cerebral, seguida por el consecuente aumento en los niveles de la saturación de oxígeno sistémica (SpO2). (51) Por lo tanto,las medidas del NIRS cerebral pueden ser un mejor indicador que la SpO2 sola para guiar la provisión de adecuada oxigenación cerebral durante el período inmediato de transición. Las medidas de NIRS cerebral no sólo disminuirán con la inadecuada oxigenación sistémica sino también por la estabilidad hemodinámica, anemia e hipocarbia. Verificar estos factores pueden tener implicancias en mejorar la oxigenación cerebral, y datos limitados han mostrado una asociación entre mediciones de la oxigenación cerebral temprana y el desarrollo de HIV (52) y los resultados del neurodesarrollo a largo plazo. (53) Se requiere más investigación para establecer los valores normativos de oxigenación cerebral para el infante pretérmino y para minimizar las diferencias en los valores de oxigenación absoluta entre varios tipo de equipos para NIRS. (54)
La estabilización temprana del infante pretérmino en la unidad de cuidados intensivos neonatales tiene también implicancias para el neurodesarrollo. Prácticas posiblemente mejores para la prevención de HIV e isquemia en el infante pretérmino han sido propuestas, (34, 55) sin embargo, el beneficio neurológico a largo plazo de adoptar tales prácticas no ha sido extensamente estudiado. Evitar situaciones de estress, limitar la manipulacióny el excesivo ruido puede ser beneficioso. (56) Una consecuencia de esta práctica sería evitar punciones lumbares de rutina en el período neonatal inmediato, pese a que no ha sido demostrado beneficioso neurológico directo de esta práctica. (34) Similarmente, la posición de la cabeza en línea media ha sido invocado como para no obstruir el flujo venoso yugular y de esta manera reducir las las fluctuaciones en la presión intracraneal y mantener un flujo cerebral más constante. (57,58) La infusión de rutina de bicarbonato de sodio para la corrección de acidosis metabólica también debería ser evitada o utilizada con extrema precaución en el infante prematuro debido a los riesgos de HIV. (59) Reduciendo el riesgo de HIV, estas prácticas pueden mejorar los resultados en el neurodesarrollo, pero más investigación es necesaria para confirmar beneficios a largo plazo.

Terapias e Intervenciones Postnatales
Indometacina

La administración de indometacina profiláctica ha sido una práctica bien estudiada, pero controvertida para el infante pretérmino. La indometacina profiláctica ha mostrado en varios estudios que reduce la incidencia de HIV severa en infantes pretérmino, (60-62) posiblemente disminuyendo el flujo sanguíneo cerebral. (63) La principal razón para el uso de la indometacina profiláctica es cerrar el ductus arterioso presistente (DAP), una complicación común en infantes MBPN. (64) Un DAP hemodinámicamente significativo aumenta el riesgo de ventilación prolongada y displasia broncopulmonar, (65) y el secuestro diastólico desde un DAP puede contribuir a alterar el flujo sanguíneo cerebral y provocar isquemia o HIV. (66) Estas consecuencias a su vez ponen al infante en mayor riesgo para déficit del neurodesarrollo. El cierre quirúrgico del DAP también ha sido asociado con déficit neurosensorial. (67) Entonces, evitar los potenciales efectos adversos de un DAP significativo con el cierre temprano con indometacina profiláctica parecería una estrategia lógica.

El Estudio de prueba de profilaxis con indometacina en pretérminos (TIPPS por sus iniciales en inglés) fue un estudio amplio, multicéntrico, randomizado conducido a través de la Red de investigación neonatal de la NICHD para investigar la utilidad de la indometacina profiláctica y enroló >1200 infantes. Este trabajo encontró que el uso de indometacina profiláctica resultó en una menor tasa de HIV severa, pero no hubo diferencia en la tasa de sobrevida sin déficit neurosensorial a los 18 meses de edad corregida. (61) Varios otros trabajos más pequeños, randomizados controlados y meta-análisis también demostraron una reducción en la HIV severa, pero ningún cambio en la sobrevida a largo plazo sin déficit neurosensorial. (9, 62)

Dada la controversia alrededor del beneficio de la indometacina profiláctica, algunos profesionales han recomendado limitar su uso a la población de alto riesgo. Los bebés MBPN cuyas madres no recibieron CAN o aquellas con corioamnionitis podrían recibir mayor beneficio de la indometacina profiláctica. (34) Otros han usado un modelo de predicción de riesgo para HIV severa con el fin de identificar una población candidata para indometacina profiláctica. (68)

El cierre temprano del DAP con indometacina profiláctica puede tener más beneficio en aquellos centros que deben transferir un número importante de infantes para ligadura de DAP. Las preocupaciones acerca de la indometacina en la alimentación temprana del MBPN y el desarrollo de perforación intestinal espontánea no fueron confirmados en un reciente estudio multicéntrico retrospectivo. (69) Dada la relativa seguridad pero falta de efecto neuroprotector a largo plazo, los centros deben tomar decisiones individualizadas acerca de la utilidad de la indometacina profiláctica para su población de prematuros.

Cafeina

La cafeína ha sido ampliamente utilizada para el tratamiento de la apnea de la prematurez, con los primeros studios demostrando efectos positivos sobre la apnea y la necesidad de apoyo ventilatorio pero con con ausencia de datos de seguridad y determinación de resultados a largo plazo. (70) El trabajo Cafeína para la Apnea de la Prematurez (CAP) fue el primero randomizado controlado en documentar un efecto beneficioso en los resultados a largo plazo para niños con PN 500-1250 gr, con reducción de muerte o discapacidad a los 18 a 21 meses de edad corregida. (71) En los infantes sobrevivientes, hubo una reducción significativa n las tasas de PC y retraso cognitivo, sin consecuencias adversas en el crecimiento. Las imágenes de Resonancia magnética (RNM) de un subgrupo de participantes del CAP demostraron mejor microestructura de la sustancia blanca, con una disminución en el coeficiente de difusión aparente y en la difusividad axial y radial, independiente de las mejoras en la morbilidad respiratoria. (72) Los estudios de seguimiento han investigado si dosis más altas de cafeína podrían conferir beneficios adicionales, con resultados mixtos. Un estudio comparó un régimen de alta dosis

(carga de 40 mg/kg, 20 mg/kg de mantenimiento comparado con 20mg/kg y 10 mg/kg respectivamente) y no se demostró efecto adverso a corto plazo, con menores tasas de fallo en la extubación. (73) Otro estudio empleando una dosis aún más alta de cafeína (80 mg/kg de carga comparada con 20mg/kg) trajo preocupación acerca de tasas más elevadas de hemorragia cerebelosa en la RMN y examen neurológico anormal a la edad equivalente al término.

Agentes Biológicos : Erytropoyetina y Darbepoetina

Los agentes estimulantes de la eritropoyesis (AEEs), como la eritropoyetina (Epo) y darbepoetina, están comenzando a mostrar beneficios no sólo como terapia para reducir las transfusiones por anemia de la prematurez, sino también por sus potenciales efectos neuroprotectores. El mecanismo específico de AEEs no está completamente comprendido, pero estudios animales apoyan un rol en la neurogénesis y la maduración de la sustancia blanca, junto con propiedades antiapoptóticas, antiinflamatorias y antioxidantes. Un trabajo inicial de Epo para el tratamiento de la anemia de la prematurez mostró que no había aumento de la tasa de PC o de la función cognitiva a los 18-22 meses de edad corregida. (74) Sin embargo, un pequeño estudio de un solo centro utilizando el mismo régimen de dosis (400 U/kg tres veces a la semana) mostró que los niños que lograron concentraciones más altas de Epo (>500 mU/mL) tuvieron Indices de Desarrollo Mental más altos. (75) Estudios recientes están mostrando una asociación más consistente entre AEEs y mejores resultados en el neurodesarrollo. Un estudio de una cohorte histórica que examinó los participantes a los 10 a 13 años de edad mostró un efecto protector global de Epo; el análisis posterior concluyó que los efectos eran atribuibles a un beneficio en aquellos niños con HIV. (76). Un estudio Fase I/II de Epo temprana a alta dosis (500, 1000, o 2500 U/kg) demostró mejor resultado cognitivo y motor sin efectos colaterales adversos. (77) Otro ensayo comparando Epo (400U/kg tres veces por semana) o darbepoetin (10 U/kg semanalmente) resultó en mejor evolución cognitiva y reducción de PC comparado con placebo. (78) El grupo Epo Suizo ha mostrado disminución de injuria cerebral y mejor desarrollo de la sustancia blanca en niños tratados tempranamente con altas dosis de Epo (3000 U/kg) apoyando estudios animales previamente publicados (79, 80); aún no han sido informados los efectos a largo plazo sobre la evolución neurológica. El entusiasmo con los AEEs particularmente los administrados tempranamente en la vida postnatal, para mejorar los resultados neurocognitivo y motor para niños extremadamente prematuros debe ser atemperado con preocupación acerca de las más altas tasas de ROP, (81) pese a que esto no fue respaldado por el estudio suizo EPO. (82) El Ensayo de Neuroprotección de la Eritropoyetina en Pretérmino (PENUT Trial por sus siglas en inglés) proveerá evidencia adicional para apoyar o refutar la seguridad y eficacia de los AEE para neuroprotección.

Conclusión

Cuando el parto prematuro es inevitable, existen una serie de intervenciones para proteger contra la potencial injuria neurológica y facilitar la reparación del cerebro pretérmino injuriado. Los esfuerzos de neuroprotección comienzan antes del nacimiento, y continúan durante el parto, resucitación y el cuidado continuo en la unidad de cuidados intensivos neonatales. Así como los procesos que documentan mejorar las infecciones asociadas a catéter (83) y la resucitación en sala de partos, (84) las medidas descriptas en este artículo podrían ser incorporadas en un "manojo de neuroprotección", con uso de checklists para asegurar un uso consistente. La implementación exitosa de todas estas intervenciones neuroprotectoras requerirá un esfuerzo coordinado entre obstetras y neonatólogos para lograr el resultado óptimo.

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Perinatal Neuroprotection for Extremely Preterm Infants

Alexis S. Davis, MD, MS Epi[1] Victoria K. Berger, MD[2] Valerie Y. Chock, MD, MS Epi[1]

[1] Division of Neonatal-Developmental Medicine, Stanford University, Palo Alto, California
[2] Division of Maternal-Fetal Medicine, University of California, San Francisco, San Francisco, California

Address for correspondence Alexis Davis, MD, MS Epi, 750 Welch Road Suite 315 Palo Alto, CA 94304 (e-mail: alexis.davis@stanford.edu).

Am J Perinatol 2016;33:290–296.

Abstract

The preterm brain is vulnerable to injury through multiple mechanisms, from direct cerebral injury through ischemia and hemorrhage, indirect injury through inflammatory processes, and aberrations in growth and development. While prevention of preterm birth is the best neuroprotective strategy, this is not always possible. This article will review various obstetric and neonatal practices that have been shown to confer a neuroprotective effect on the developing brain.

Keywords

- very low-birth-weight
- brain injury
- neuroprotection
- outcomes
- premature infant

Despite improvements in the rate of preterm birth in the last several years, the proportion of very low-birth-weight (VLBW) infants in 2013 remained steady in the United States at 1.4% of live births.[1] In absolute numbers, this translates into approximately 55,000 infants born at risk for neurologic injury each year. Risk factors for adverse neurodevelopmental outcome in this vulnerable population include direct neurologic injury such as intraventricular and intraparenchymal hemorrhage,[2,3] and indirect harm resulting from inflammation or infection.[4,5] Up to 30% of extremely low-birth-weight (ELBW) infants with normal neuroimaging may be at risk for adverse outcome,[6] suggesting a role for insult at the cellular level with alterations in growth[7] and connectivity[8] in the developing brain.

Early attempts to improve neurologic outcomes in preterm infants were targeted at preventing injury by reducing the rate of intraventricular hemorrhage (IVH). While the initial effects of antenatal phenobarbital and indomethacin prophylaxis seemed favorable in the neonatal period, they did not have a significant impact on subsequent neurodevelopmental outcomes.[9,10]

Prevention of preterm birth and extension of gestation through antenatal progesterone, prophylactic cerclage, and judicious application of artificial reproductive technology is the ultimate strategy to reduce the rates of infants surviving with neurologic sequelae.[11] If preterm birth cannot be prevented, however, several interventions exist to reduce the risk of adverse outcome in extremely preterm infants. This review will describe strategies in the antepartum period, during resuscitation and transition to extrauterine life, and postnatal therapies to reduce the risk of adverse outcome (►**Table 1**).

Antenatal Strategies for Neuroprotection

Antenatal Corticosteroids

Antenatal corticosteroid (ACS) use in the setting of suspected premature birth was first described 1972 by Liggins and Howie, who demonstrated the effectiveness of corticosteroids in reducing respiratory distress syndrome and IVH among premature babies.[12] Following the introduction of ACS, more studies emerged showing similar favorable outcomes.[13,14] A Cochrane review showed a significant reduction in those that received ACS prior to preterm delivery.[15] Given the important role of ACS, the National Institutes of Health published a consensus statement in 1995 recommending that ACS be offered to patients at risk for delivery between 24 and 34 weeks.[16] A more recent study that evaluated outcomes of extremely preterm infants born at less than 29 weeks concluded that IVH was less likely among those that received ACS.[17] Administration of ACS to women at risk for preterm birth is thought to be the most beneficial intervention

received
November 18, 2015
accepted
November 24, 2015
published online
January 22, 2016

DOI http://dx.doi.org/10.1055/s-0035-1571148.
ISSN 0735-1631.

Table 1 Proposed checklist for neuroprotective strategies in the preterm infant

Antepartum
Antenatal steroids[18] • Gestational age <34 wk • Recommended dosing: betamethasone 12 mg q24h × 2 doses or dexamethasone 6 mg q12h × 4 doses • Consider rescue course if undelivered and preterm delivery <34 wk expected Magnesium sulfate[33] • Gestational age <32 wk • Dosing recommendations vary
Delivery and initial care
Delayed cord clamping[42] • For preterm infants, specific gestational age criteria not specified • 30–60 s recommended • Position infant at or below the level of the placenta
NICU care considerations[34,55,59]
• Midline head positioning • Delay procedures requiring excessive handling, e.g., lumbar puncture • Avoid sodium bicarbonate infusions • Near-infrared spectroscopy monitoring of cerebral oxygenation
Convalescent care in the NICU
Prophylactic indomethacin[61] • Consider in high-risk populations • Suggested dose: 0.1 mg/kg q24h × 3 doses Caffeine[71] • Infants <1,250 g • Loading dose 20 mg/kg followed by maintenance 5–10 mg/kg daily Erythropoiesis stimulation agents: erythropoietin or darbepoetin • Optimal population and dosing not well established

available to obstetricians in reducing neonatal respiratory and neurologic morbidity.[18]

Although short-term benefits of ACS administration have been widely appreciated, the long-term neurodevelopmental effects have been questioned, and studies have shown variable results. Lower rates of death or neurodevelopmental impairment at 18 to 22 months' corrected age were reported by the Neonatal Research Network among infants born at 23 to 25 weeks, including significant improvements in the rates of death, IVH, and periventricular leukomalacia.[19] In a 30-year follow-up of the Auckland steroid trial, there was no difference in cognitive outcomes between infants exposed to ACS and those exposed to placebo,[20] and this was true in the Cochrane meta-analysis.[15] However, a more recent meta-analysis, which included 14 studies on long-term neurodevelopmental effects of ACS, showed a favorable outcome, with a reduction in cerebral palsy among infants born before 34 weeks.[21] Importantly, a decrease in risk of severe disability was demonstrated in the most premature infants, born at less than 28 weeks, with 34% prevalence of severe disability in the steroid exposure group compared with 44% in those untreated.[21]

Given the documented decreased risk of respiratory and neurologic morbidity when ACS are administered, current practice guidelines recommend a course of ACS when preterm birth is suspected, with either two 12-mg betamethasone intramuscular injections given 24 hours apart or four 6-mg dexamethasone intramuscular injections given 12 hours apart.[18] Emerging evidence suggests that consideration should be given to one rescue course if the mother, who originally received ACS but was undelivered, is again at risk for delivery before 34 weeks.[18,22] Repeat doses beyond one rescue course are not recommended, as repeat doses have been associated with decrease in fetal growth and head circumference.[23,24]

Magnesium Sulfate

An association of magnesium sulfate with improved neurologic outcomes was first recognized through studies of infants born to preeclamptic mothers exposed to magnesium sulfate demonstrating lower rates of IVH and cerebral palsy (CP).[25–27] In 2003, a trial showed a nonsignificant trend toward decrease rates of CP with magnesium sulfate exposure among infants delivered before 30 weeks.[28] More recently, a trial of infants born between 24 and 31 weeks demonstrated a significant reduction in the rate of CP for infants exposed to magnesium sulfate (1.9 vs. 3.5%).[29] A Cochrane review published in 2009 concluded that although there was no decrease in mortality, there was a reduction in CP and gross motor dysfunction among infants exposed to magnesium sulfate, with the number of mothers needed to treat of 63.[30] The precise mechanism by which magnesium sulfate exerts a neuroprotective benefit is not known, but it is speculated that it possess anti-inflammatory and anti-excitotoxic effects while also improving cerebral blood flow and stabilizing fluctuations in blood pressure in the newborn

infant.[31] A recent study of infants ≤30 weeks' gestational age using near infrared spectroscopy (NIRS) showed that those exposed to antenatal magnesium sulfate had lower cerebral fractional tissue oxygen extraction in the first 24 hours of life compared with nonexposed infants.[32] The authors speculated that magnesium sulfate exerted a neuroprotective effect by reducing cerebral metabolic demand. In response to the growing evidence demonstrating reduction in CP rates, the American College of Obstetricians and Gynecologists (ACOG) with the Society for Maternal Fetal Medicine issued a statement in support of magnesium sulfate for neuroprotection in women at risk for delivery under 32 weeks' gestation.[33]

Delivery Room Management and Care during the Transition to Postnatal Life

Specific strategies and interventions in the delivery room to preserve long-term neurodevelopment of the preterm infant remain an important goal. Several areas of current research include ideal oxygen saturation targets in the first few minutes of life, optimal approaches to ventilation and initial lung-distending pressures, practices to best avoid hypothermia, and efforts to minimize the need for cardiac compressions and extensive resuscitation.[34] We will not focus on delivery-room-specific interventions, as this will be addressed in another companion article in this series, aside from addressing the practice of delayed umbilical cord clamping as it pertains to preterm infants.

Delayed Cord Clamping

Delayed cord clamping (DCC), also known as timed umbilical cord clamping or placental transfusion, has experienced several eras of research interest and definitional shifts.[35] In the premodern era of medicine, "early" cord clamping was defined as occurring at approximately 1 minute of life, and delayed clamping occurring at or after 5 minutes. Modern operational definitions seem to equate early with immediate clamping, in the first 15 seconds of life; the timing of DCC varies by study, between 30 seconds and up to 1 to 5 minutes of life. In the 1960s and 1970s, DCC was demonstrated to reduce the incidence of RDS in preterm infants, an observation initially noted by veterinarians as the "Barker Foal Syndrome" and borne out in other animal models. DCC lost favor in the postsurfactant era, as the emphasis in care for extremely preterm infants was redirected toward initiating resuscitative efforts as soon as possible and due to concerns about hyperbilirubinemia and hyperviscosity in those exposed to DCC.

We have come full circle, and interest in DCC has been renewed with multiple clinical trials in preterm infants aimed at the prevention of anemia of prematurity. A Cochrane Review in 2004 reviewed seven studies conducted largely in the 1980s and 1990s and affirmed the benefit of DCC in infants less than 37 weeks by reducing the need for red blood cell transfusions, improving blood pressure, and decreasing the rate of IVH.[36] More trials and meta-analyses have confirmed the hematologic and physiologic benefits of DCC, generally without adverse effects such as low Apgar scores, acidosis, or hypothermia.[37–40] There is speculation that DCC may confer additional immunologic and regenerative benefits through transfer of stem cells to ameliorate various neonatal morbidities as well as age-related diseases.[41] Due to the mounting body of literature, ACOG published a Committee Opinion in 2012 that recommended DCC up to 60 seconds for preterm infants but cited that areas requiring additional investigation included determining the optimal timing by mode of delivery (vaginal vs. cesarean section) and risks and benefits conferred to the most premature infants (defined as <28 weeks' gestational age).[42] Reports of the long-term benefits of DCC in preterm infants are sparse and have yet to demonstrate a significant benefit on neurodevelopmental outcomes.[39] However, a 4-year outcomes study of DCC in a low-risk, term infant population demonstrated improvements in fine motor and social domains, particularly in boys.[43]

DCC is most effective when onset of respirations has already occurred, thereby permitting the pulmonary vascular bed to fill with blood.[44] Additional variables to optimize placental transfusion include the position of the infant relative to the placenta to permit optimal gravitational flow and the presence of uterine contractions, including the administration of oxytocin.[45] Current areas of active research include (1) umbilical cord milking, either to enhance placental transfusion or when resuscitation efforts need to be initiated before DCC can occur,[46,47] and (2) the development of mobile trolleys to initiate resuscitation and provide respiratory support prior to clamping the umbilical cord.[48] Further, additional data on the long-term outcomes to support or refute the benefits of DCC are needed.

Resuscitation Practices and Neuromonitoring after Birth

Neuromonitoring in the delivery room with NIRS may help to guide resuscitation to improve neurodevelopmental outcomes. NIRS is a noninvasive method to continuously monitor cerebral tissue oxygenation and can feasibly be applied to preterm infants during resuscitation in the first few minutes of life.[49] Preterm infants requiring respiratory support in the delivery room have been shown to have lower cerebral tissue oxygenation levels compared with those requiring no intervention.[50] Furthermore, effective ventilatory resuscitation after birth in preterm infants results first in increased cerebral tissue oxygenation, followed by a subsequent increase in systemic oxygen saturation (SpO_2) levels.[51] Therefore cerebral NIRS measures may be a better reflection than SpO_2 alone to guide adequate cerebral oxygen delivery during the immediate transition period. Cerebral NIRS measures will be decreased not only with inadequate systemic oxygenation, but also by hemodynamic stability, anemia, and hypocarbia. Addressing these factors may have implications in improving cerebral oxygenation, and limited data have demonstrated an association between early cerebral oxygenation measures and the development of IVH[52] and longer-term neurodevelopmental outcomes.[53] Further research is required to establish normative cerebral oxygenation values for the preterm infant and to minimize differences in absolute oxygenation values between various types of NIRS devices.[54]

Early stabilization of the preterm infant in the neonatal intensive care unit has further implications for neurodevelopment. Potentially better practices for the prevention of IVH and ischemia in the preterm infant have been promoted[34,55] however, the long-term neurologic benefit of adopting such practices has not been extensively studied. Avoiding stressful conditions and limiting handling and excessive noise may be of benefit.[56] A consequence of this practice would be to avoid routine lumbar punctures in the immediate newborn period, although no direct neurologic benefit of this practice has been demonstrated.[34] Similarly, midline head positioning has been advocated so as not to impede jugular venous flow and thereby reduce fluctuations in intracranial pressure and maintain a more constant cerebral blood flow.[57,58] Routine sodium bicarbonate infusion for correction of metabolic acidosis should also be avoided or used with extreme caution in the preterm infant due to risks of IVH.[59] By reducing the risk of IVH, these practices may improve neurodevelopmental outcomes, but further research must be conducted to confirm long-term benefit.

Postnatal Therapies and Interventions

Indomethacin

The administration of prophylactic indomethacin has been a well-studied, but controversial, practice for the preterm infant. Prophylactic indomethacin has been shown in multiple studies to reduce the incidence of severe IVH in preterm infants,[60–62] possibly by decreasing cerebral blood flow.[63] Further rationale for use of prophylactic indomethacin is to close the persistent patent ductus arteriosus (PDA), a common complication in ELBW infants.[64] A hemodynamically significant PDA increases the risk of prolonged ventilation and bronchopulmonary dysplasia,[65] and diastolic steal from a PDA may contribute to altered cerebral blood flow and ensuing ischemia or IVH.[66] These consequences in turn put an infant at higher risk for neurodevelopmental impairment. Surgical ligation of a PDA has further been associated with neurosensory impairment.[67] Thus, avoiding the potential adverse outcomes of a significant PDA by early closure with prophylactic indomethacin would appear to be a logical strategy.

The Trial of Indomethacin Prophylaxis in Preterms Study (TIPPS) was a large, randomized multicenter study conducted through the NICHD Neonatal Research Network to investigate the utility of indomethacin prophylaxis and enrolled >1,200 ELBW infants. This trial found that use of prophylactic indomethacin resulted in a lower rate of severe IVH, but no difference in survival without neurosensory impairment at 18 months corrected age.[61] Several other smaller, randomized controlled trials and a meta-analysis also demonstrated a reduction in severe IVH, but no change in long-term survival without neurosensory impairment.[9,62]

Given the controversy surrounding the benefit of prophylactic indomethacin, some practitioners have advocated for limiting its use to a high-risk population. VLBW infants whose mothers did not receive ACS or those with chorioamnionitis might have greater benefit from prophylactic indomethacin.[34] Others have used a risk prediction model for severe IVH to target a population for prophylactic indomethacin.[68] Early PDA closure with prophylactic indomethacin may have further benefit in centers that transport a significant number of infants out for PDA ligation. Concerns about the use of prophylactic indomethacin in early feeding of ELBW infants and the development of spontaneous intestinal perforation were not borne out in a recent multicenter retrospective study.[69] Given the relative safety but lack of long-term neuroprotective effect, centers must make individualized decisions about the utility of prophylactic indomethacin for their preterm population.

Caffeine

Caffeine has widely been used for the treatment of apnea of prematurity, with early studies demonstrating positive effects on apnea and need for ventilator support but lacking in safety data and assessment of long-term outcomes.[70] The Caffeine for Apnea of Prematurity (CAP) Trial was the first randomized controlled trial to document a beneficial effect on longer-term outcomes for infants 500 to 1,250 g birth weight, with reduced death or disability at 18 to 21 months' corrected age.[71] In surviving infants, there was a significant reduction in the rates of CP and cognitive delay, without adverse consequences on growth. Magnetic resonance imaging (MRI) of subset of CAP Trial participants demonstrated improved white matter microstructure, with a decrease in apparent diffusion coefficient and axial and radial diffusivity, independent of improvements in respiratory morbidity.[72] Follow-up studies have investigated whether higher doses of caffeine might confer additive beneficial effects, with mixed results. One study compared high-dose regimen (40 mg/kg caffeine load, 20 mg/kg maintenance therapy compared with 20 and 10 mg/kg, respectively) and demonstrated no adverse short-term effects, with lower rates of extubation failure.[73] Another study using an even higher dose of caffeine (80 mg/kg loading dose compared with 20mg/kg) raised concern about higher rates of cerebellar hemorrhage on MRI and abnormal neurologic exam at term equivalent.

Biologic Agents: Erythropoietin and Darbepoetin

Erythropoiesis-stimulating agents (ESAs), such as erythropoietin (Epo) and darbepoetin, are beginning to show promise not only as a therapy for reducing transfusions for anemia of prematurity, but also for their potential neuroprotective effects. The specific mechanism of ESAs is not completely understood, but animal studies support a role in neurogenesis and white matter maturation, along with antiapoptotic, anti-inflammatory, and antioxidant properties. An early trial of Epo for the treatment of anemia of prematurity showed no improvement in the rates of cerebral palsy or cognitive function at 18 to 22 months' corrected age.[74] However, a small single-center study using the same dosing regimen (400 U/kg three times per week) showed that infants who achieved higher Epo concentrations (>500 mU/mL) had higher Mental Developmental Index scores.[75] Recent studies are showing a more consistent association between ESAs and improved neurodevelopmental outcomes. One historical

cohort study that examined participants at 10 to 13 years of age showed an overall protective effect of Epo; further analysis concluded that the effects were attributable to a benefit in those infants with IVH.[76] A phase I/II study of early, high-dose Epo (500, 1,000, or 2,500 U/kg) demonstrated improved cognitive and motor outcomes without adverse side effects.[77] Another trial comparing Epo (400 U/kg three times per week) or darbepoetin (10 U/kg weekly) resulted in improved cognitive outcomes and reduced CP compared with placebo.[78] The Swiss EPO group has shown reduced brain injury and improved white matter development in infants treated with early, high-dose Epo (3,000 U/kg), substantiating previously published animal studies[79,80]; long-term effects on neurologic outcomes have not yet been reported. Enthusiasm about ESAs, particularly those given early in postnatal life, to improve neurocognitive and motor outcomes for extremely preterm infants must be tempered with concern about higher rates of retinopathy of prematurity,[81] though this was not substantiated in the Swiss EPO study.[82] The Preterm Erythropoietin Neuroprotection Trial (PENUT Trial, NCT01378273) will provide additional evidence to support or refute the safety and efficacy of ESAs for neuroprotection.

Conclusion

When preterm birth is inevitable, a series of interventions exist to protect against potential neurologic injury and to enhance repair of the injured preterm brain. Neuroprotection efforts begin before birth and continue through delivery, resuscitation, and continuing care in the neonatal intensive care unit. Much like processes documented to improve catheter-associated bloodstream infections[83] and delivery room resuscitation,[84] the measures described in this article could be incorporated into a "neuroprotection bundle," with use of a checklist to ensure consistent use. Successful implementation of all of these neuroprotective interventions will require a coordinated effort between obstetricians and neonatologists to achieve the most optimal outcome.

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