Presión sanguínea temprana, terapia anihipotensora y resultados a los 18-22 meses de edad corregida en infantes extremadamente pretérmino

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ABSTRACT

Objetivo: Investigar las relaciones entre cambios tempranos de presión sanguínea (PS), recepción de terapia antihipotensora y resultados a los 18-22 meses de edad corregida (EGC) en infantes extremadamente pretérmino.

Diseño: Estudio prospectivo observacional de infantes de 230/7-266/7 semanas de edad gestacional (EG). Se registraron los valores horarios de PS y la exposición a terapia antihipotensora en las primeras 24 horas. Se definieron cuatro grupos: infantes que recibieron y que no recibieron antihipotensores en quienes la PS subió o no al ritmo esperado (definido como un incremento en la presión media arterial de ≥5 mmHg/día). Se utilizó un modelo randomizado controlando para la agrupación central, EG y severidad de la enfermedad para investigar la relación entre PS, terapias antihipotensoras y resultados del infante.

Ámbito: Dieciséis centros académicos del Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Principales medidas de resultado: Muerte o déficit del neurodesarrollo/retraso madurativo (DNRM) a los 18-22 meses de EC.

Resultados: de 367 infantes, 203 (55%) recibieron terapia antihipotensora, 272 (74%) sobrevivieron hasta el alta y 331 (90%) tuvieron un resultado conocido a los 18-22 meses de EC. Con la regresión logística, hubo un riesgo aumentado de muerte/ DNRM con la terapia antihipotensora versus no tratamiento (OR 1.836, IC 95% 1.092 a 3.086), pero no DNRM aislado (OR 1.53, IC 95% 0.708 a 3.307).

Conclusiones: La exposición a terapia antihipotensora, independiente de los cambios de PS tempranos, estuvo asociada con riesgo aumentado de muerte /DNRM a los 18-22 meses de EC cuando se controló para factores de riesgo que se sabe afectan sobrevida y neurodesarrollo.

INTRODUCCIÓN

Muchas investigaciones en los últimos 25 años sugieren que los infantes pretérmino considerados hipotensos en el período postnatal inmediato están en riesgo aumentado para resultados adversos. (1-14) Esta observación ha llevado a algunos clínicos a administrar terapias en un esfuerzo para elevar la PS arterial y presumiblemente, mejorar las posibilidades de sobrevida del infante sin morbilidad mayor (12-16). Hasta la fecha, no se ha observado tal mejora en los resultados (1-16). Más preocupante es la posibilidad de que los antihipotensores comúnmente prescriptos puedan aumentar los riesgos en los niños prematuros (3, 7, 12-14).

La fisiología en desarrollo del infante extremadamente pretérmino y la naturaleza dinámica del sistema cardiovascular son algunos de los desafíos inherentes en la investigación del manejo de la PS en el período neonatal inmediato. El amplio rango de valores de PS observados en cualquier hora postnatal y el espontáneo ascenso en PS que típicamente ocurre después del nacimiento (5, 8, 9) hacen difícil determinar si un valor de PS para un niño determinado en una edad postantal específica es demasiado elevado, demasiado bajo, aumenta demasiado rápido o no aumenta suficientemente rápido. No hay trabajos randomizados controlados con placebo para guiar las decisiones terapéuticas (3, 17-19). Así, el manejo de la PS para esta población varía considerablemente con un amplio rango en la frecuencia administración de terapia antihipotensora para la percepción de baja PS (12-14, 16).

Los datos sobre la relación entre el manejo temprano de la PS y DNRM son insuficientes y difíciles de interpretar. Esto está relacionado en parte al limitado número de estudios reportando tasas de DNRM, el tamaño muestral, los datos sobre terapias específicas antihipotensoras y poblaciones heterogéneas en estudio (9-11).

Qué se sabe acerca de este tema

- Los infantes extremadamente pretérmino que reciben terapia antihipotensora tienen peores resultados en internación.
- La relación entre los resultdos a la edad infantil, valores de presión sanguínea y terapias antihipotensoras no es clara
- Investigar estas relaciones es desafiante en parte porque los cambios en valores de PS ocurren poco después del nacimiento.

Qué agrega este trabajo

- Los niños que recibieron terapia antihipotensora tuvieron mayor posibilidad de tener desarrollo deficitario o retrasado que los infantes no tratados sin importar si la PS aumentaba.
- Estos resultados no pueden ser explicados por diferencias en los marcadores de severidad de enfermedad investigados.

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determinar si los resultados del infante después de la administración de antihipotensores están relacionados a aumento de la PS en conjunción con la terapia. Los objetivos de este estudio fueron evaluar los resultados en la primera infancia en una cohorte de infantes pretérmino divididos en grupos según los cambios tempranos en la PS y recepción de antihipotensores en un esfuerzo por clarificar: 1) si los resultados adversos en infantes con PS preocupante están relacionados a la falta de tratamiento antihipotensor y 2) si la sobrevida y/o el neurodesarrollo intacto en infantes tratados están relacionados al aumento en la PS.

MÉTODOS

Este estudio reporta los resultados a los 18-22 meses de edad corregida (EC) para infantes enrolados en un estudio prospectivo observacional de niños nacidos extremadamente pretérmino a las 236/7- 266/7 semanas de edad gestacional (EG) en 16 centros académicos del Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) enrolados desde el 21 de Julio de 2010 hasta el 21 de Enero de 2011. Una detallada descripción de la población de pacientes, explicación del proceso de consentimiento informado y de los resultados intrahospitalarios han sido reportados previamente (8, 14).

Brevemente, se registraron las mediciones horarias de PS (tanto invasiva como no invasivas) y la administración de todos los tratamientos antihipotensores en las primeras 24 horas. Terapia antihipotensora incluyó fluído en bolo (≥10 ml /kg de cristaloide), dopamina, dobutamina, hidrocortisona, epinefrina o cualquier derivado de sangre.Todas las decisiones terapéuticas fueron hechas por el equipo clínico a cargo. Los infantes nacidos a las 23-26 semanas de EG ingresados a UCIN fueron incluidos en este estudio. Fueron excluídos los niños que murieron en sala de partos, los que nacieron con un defecto mayor congénito o se les retiró el cuidado intensivo poco después del nacimiento porque el equipo de cuidado clínico consideró que la situación era desesperante. Este estudio fue aprobado por el comité de revisión institucional de cada centro participante. En dos centros, los infantes fueron enrolados después de que sus padres firmaron un consentimiento informado específico del estudio. En los restantes 14 centros, este estudio fue incorporado en el estudio de Base de datos Genérica (GDB) permanente del NRN porque todos los infantes de este estudio califican para ser incluidosen la GDB (en base a su EG al nacer), y ambos estudios recopilaron información sin identificar al paciente. El Comité institucional de revisión de algunos centros NRN autorizó la recolección de datos para GDB con una forma de consentimiento (8).

El resultado primario para esta investigación fue la incidencia de muerte o DNRM a los 18-22 meses de EC. DNRM se definió como un score cognitivo o motor <70 en la Escala de Desarrollo Infantil Bayley, 3ª Edición (20), parálisis cerebral (puntaje en Sistema de Clasificación de Función Motora Gruesa >2) (21), déficit auditivo requiriendo equipamiento auditivo en ambos oídos o ceguera (visión no útil en algún ojo). Resultados secundarios fueron las tasas de cualquier DNRM y componentes individuales de DNRM entre los infantes que sobrevivieron hasta los 18-22 meses de EC. Los resultados fueron comparados entre cuatro grupos de infantes definidos por la administración de tratamiento antihipotensor y el ritmo de aumento en la PS: 1) infantes que no recibieron un tratamiento antihipotensor en los cuales la PS aumentó según lo esperado, 2) infantes no tratados en los cuales la PS no aumentó al ritmo esperado, 3) infantes que recibieron un tratamiento antihipotensor en las primeras 24 horas en quienes la PS aumentó al ritmo esperado y 4) niños tratados que no tuvieron el aumento esperado de la PS. El aumento esperado en la PS fue definido a priori como un aumento en la PS arterial media de ≥5 mmHg desde la hora postnatal 4 hasta la hora postnatal 24.Esta definición fue elegida porque este ritmo de aumento fue reportado previamente para los infantes extremadamente pretérmino, este fue el ritmo promedio de aumento en la PS arterial para esta cohorte de infantes, el ritmo promedio fue el mismo para cada semana de gestación a través de todo este rango de EG y el ritmo promedio para esta cohorte fue el mismo para los pacientes que recibieron versus los que no recibieron un tratamiento antihipotensor (5, 8).

Los análisis de datos fueron realizados en el Centro de Coordinación de Datos del NRN (RTI International, Research Triangle Park, North Carolina, USA). El análisis estadístico se realizó utilizando el software SAS V 9.3 (SAS Institute, Cary, North Carolina, USA). Para el análisis univariado, se utilizaron los tests X2 o exacto de Fisher para comparar proporciones y el análisis de varianza se utilizó para comparación de medias. Modelos de regresión logística que incluyeron un intercepto aleatorio para representar el potencial agrupamiento central, fueron estimados para los resultados muerte/ DNRM y DNRM (sólo). Las covariables de EG alnacer y severidad de la enfermedad fueron utilizados en adición a exposición a la terapia antihipotensora (tratados vs no tratados) y los cambios tempranos en la PS (ritmo esperado de elevación vs ritmo menor al esperado de elevación) (14). Severidad de la enfermedad fue definida como el número acumulativo de cualquiera de los siguientes: Apgar al minuto ≤3, presencia de anemia temprana (hematocrito inicial ≤30%), cualquier pH <7.10 en las primeras 24 hrs postnatales, hemocultivo positivo (obtenido dentro de las primeras 72 horas de vida) o compresiones cardíacas en sala de partos (14).

RESULTADOS

Fueron enrolados en el estudio 367 infantes (Figura 1). De estos, 158 sobrevivieron a las primeras 24 horas sin recibir un tratamiento antihipotensor, incluyendo 91 (58%) en los cuales la PS media arterial aumentó ≥5 mm Hg y 67 (42%) en los cuales no hubo tal aumento. La PS se elevó según lo esperado en 128 (65%) de los 198 infantes que recibieron tratamiento antihipotensor. De los 203 infantes que recibieron tratamiento antihipotensor, 135 (67%) recibieron un fluído en bolo, 102 (50%) recibieron un producto sanguíneo y 92 (45%), 25 (12%), 18 (9%) y 1 (<1%) recibieron dopamina, hidrocortisona, dobutamina y vasopresina respectivamente. Cinco infantes que recibieron un tratamiento antihipotensor fallecieron en las primeras 24 horas. Las variables intrahospitalarias y los datos de resultado para las cuatro cohortes son presentadas en la Tabla 1 (ver en el original).

Los resultados a los 18-22 meses de EC (muerte o estado del Neurodesarrollo) se conocieron para 331 (90%) infantes. Esto incluyó 99 infantes que fallecieron y 232 que tuvieron pruebas del neurodesarrollo. Treinta y seis niños se perdieron para el seguimiento. No hubo diferencias significativas en las morbilidades intrahospitalarias conocidas entre los pacientes perdidos para el seguimiento y los sobrevivientes con resultados conocidos a los 18-22 meses. En el análisis univariado, muerte o DNRM fue significativamente más alto en los niños tratados comparados con los no tratados (Tabla 2-Ver en el original) sin importar si la PS subió según lo esperado. Las tasas de componentes individuales de DNRM variaron entre los cuatro grupos, pero estas diferencias no alcanzaron significancia estadística (Tabla 2; $p>0.05$ para cada uno). Hubo diferencias significativas en la incidencia de DNRM o el resultado compuesto muerte/DNRM en los modelos de regresión logística para efectos aleatorios (Tabla 3- Ver en el original). Por cada semana de aumento en la EG al nacer, la factibilidad de ambas DNRM y muerte/DNRM disminuyó. La presencia de cualquier marcador de severidad aumentó las posibilidades de ambos DNRM y muerte/DNRM al igual que el número acumulado de indicadores de severidad de la enfermedad. Cuando se incorporaron estas variables y los cambios en PS a los modelos de regresión, el tratamiento con cualquier terapia antihipotensora fue un significativo predictor de muerte/DNRM, pero no de DNRM aislado. En modelos de regresión similares incorporando el tratamiento antihipotensor, el aumento en PS (al ritmo esperado vs menos que el ritmo esperado) no estuvo significativamente asociado con ninguno
de los resultados

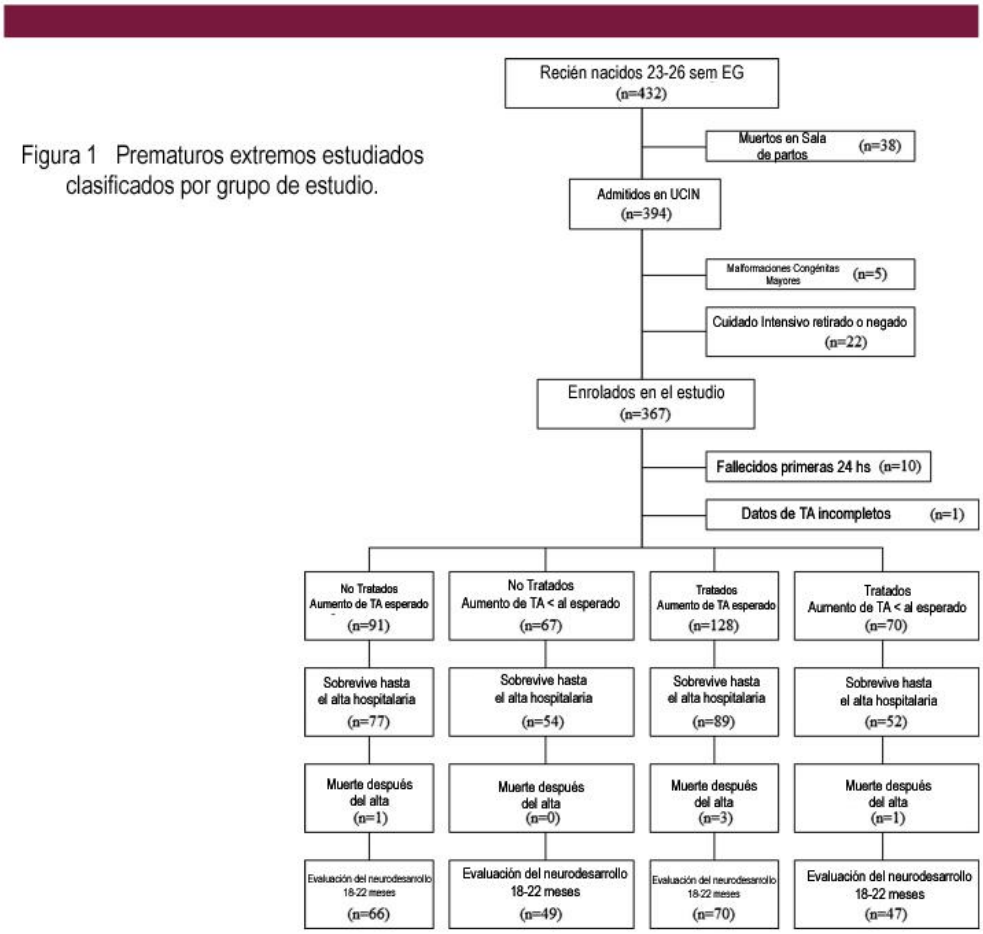

Figura 1 Prematuros extremos estudiados clasificados por grupo de estudio.

DISCUSIÓN

Los estudios previos examinando la relación entre manejo temprano de la PS y los resultados en el niño evaluaron infantes hipotensos vs normotensos ó infantes con hipotensión tratados vs no tratados (6, 9-11). Hipotensión fue definida como recepción de tratamiento antihipotensor (independiente de los valores de PS) o un valor de PS por debajo de un límite numérico (ej. PS arterial media menor que o igual al equivalente numérico de la EG del infante), que no necesariamente fue usado clínicamente.

Las dificultades inherentes a la investigación del manejo temprano de PS incluyen el aumento espontáneo en la PS que ocurre después del nacimiento, la correlación positiva entre valores de

PS y EG al nacer, y el amplio rango de valores de PS observado en cualquier hora específica postnatal en todos los rangos de EG (5, 6, 8). Los hallazgos de este estudio subrayan la importancia de considerar múltiples factores cuando se examina la PS en relación a los resultados del infante.

Los infantes que recibieron un tratamiento antihipotensor tuvieron una mayor tasa de muerte/DNRM independiente de los cambios tempranos en la PS. El significado de este hallazgo permanece poco claro. Es posible que parámetros diferentes a un límite numérico para baja PS puedan identificar mejor infantes en riesgo para resultados deficitarios que se beneficiarían con el tratamiento. La incorporación de medidas indirectas del flujo sanguíneo sistémico o cerebral también pueden parcialmente explicar la variabilidad observada en el manejo de la PS, incluyendo por qué algunos niños sin baja PS recibieron un tratamiento antihipotensor, mientras que otros con baja PS no lo recibieron (3, 14, 22, 23).

Pese a no ser estadísticamente significativo (p= 0.055) hubo una tendencia hacia mayor mortalidad en niños tratados (29%) versus no tratados (17%) en este estudio, independiente del ritmo de ascenso en la PS. Otros reportes han sugerido también que los infantes que reciben terapia antihipotensora tienen una tasa mayor de mortalidad (5-7, 24). Conclusiones definitivas sobre esta asociación no pueden ser hechas dado que hasta la fecha, no existen trabajos randomizados.

Tabla 1. Variables intrahospitalarias y resultados relacionados con Tratamiento antithipotensor y aumento de TA.

	No Tratados Aumento de TA esperado n=91	No Tratados Aumento de TA < al esperado n=67	Tratados Aumento de TA esperado n=128	Tratados Aumento de TA < al esperado n=70	Valor p
Peso al nacer (grs), media +/- DE	784±165	750±144	692±150	713±168	<0.001
EG al nacer (sem), media +/- DE	25.5±0.9	25.6±1.0	25.1±1.1	25.3±1.0	<0.001
Esteroide Prenatal, n (%)	81 (89)	61 (91)	118 (92)	65 (93)	0.814
Indicador de severidad de enfermedad, n (%)	37 (41)	37 (55)	93 (73)	56 (80)	<0.001
Apgar 1 min <=3	33 (36)	33 (49)	79 (62)	49 (70)	<0.001
Compresión torácica en Sala de Partos	5 (5)	7 (10)	14 (11)	8 (11)	0.5
Hemocultivo inicial +	0	0	3 (2)	5 (7)	0.01
pH < 7.1 en primeras 24 hs	1 (1)	3 (4)	13 (10)	11 (16)	0.003
primer Hcto < 30%	4 (4)	3 (4)	25 (20)	12 (17)	<0.001
HIV o LMPV severa, n (%)	11(12)	8 (13)	28 (23)	21 (31)	0.008
ECN que requiera Cirugía, n (%)	4(5)	2 (4)	6 (7)	2 (4)	0.881*
Intervención por ROP, n (%)	9 (12)	6 (11)	18 (20)	14 (27)	0.071
DBP, n (%)	40 (51)	36 (63)	58 (62)	34 (62)	0.402
Sobrevida al alta hospitalaria	77 (85)	54 (81)	89 (70)	52 (74)	0.055

* La prueba exacta de Fisher. EG= edad gestacional TA= Tensión Arterial, HIV=Hemorragia Intraventricular LMPV= Leucomalacia Periventricular ECN= Enterocolitis Necrotizante ROP= Retinopatía del Prematuro DBP= Displasia Broncopulmonar

Potenciales confundidores incluyen mayor severidad de la enfermedad en los bebés tratados, una mayor probabilidad de una condición conocida por aumentar la mortalidad (ej. Sepsis), inclusión de infantes “in extremis” que recibieron un tratamiento antihipotensor, pero eran proclives a morir independientemente del grado de soporte terapéutico provisto y omisión de otros factores que pueden predisponer al infante tanto para ser percibido como con baja PS que requiere intervención y muerte (tales como bajo score de Apgar o acidosis temprana). Se hicieron intentos de controlar estos aspectos en el presente estudio tales como excluir niños considerados terminalmente enfermos en las primeras 24 horas e incorporar la severidad de la enfermedad en el análisis de regresión utilizando factores que impactan en el manejo de la PS y están asociados con menor sobrevida(14).

En un estudio previo multicéntrico, estudio ELGAN los investigadores evaluaron la relación entre indicadores y tasas de DNRM a los 24 meses de EC (9). Similar a este estudio, los investigadores

encontraron poca evidencia de una asociación entre los valores tempranos de PS y el subsiguiente neurodesarrollo. Otros estudios informaron similares hallazgos (10, 11, 18). La asociación entre tratamiento antihipotensor y pérdida auditiva informada por Fanaroff y otros (6) no fue observada en esta investigación, posiblemente debido a la baja tasa general de sordera (<3%).

Los datos de este y otros estudios demuestran la compleja relación entre manejo de la PS, mortalidad y neurodesarrollo. Muerte y DNRM son resultados distintos, y es posible que las circunstancias que llevan a la muerte sean distintas pero superpuestas con factores que llevan a la injuria cerebral tales como estas terapias- o factores que influencien la decisión de administrarlas- puedan influenciar el riesgo de mortalidad en forma diferente a como influencian el riesgo de DNRM (25, 26). Alternativamente, factores más allá del período postnatal inmediato pueden tener mayor influencia en los resultados de la primera infancia enmascarando entonces el impacto del manejo de la PS en el neurodesarrollo (25). Finalmente, dada la complejidad del sistema cardiovascular inmaduro, las terapias antihipotensoras pueden influenciar influenciar la función cardíaca de forma tal que ellas no alteran uniformemente el flujo sanguíneo cerebral postnatal temprano o la entrega de oxígeno (18, 22, 25).

Tabla 2 Resultados ND a los 18-22 meses relacionados con la administración de terapia antihipotensora y aumento de la TA esperado.

	No Tratados Aumento de TA esperado n=91	No Tratados Aumento de TA < al esperado n=67	Tratados Aumento de TA esperado n=128	Tratados Aumento de TA < al esperado n=70	Valor p
Muerte o algún deterioro del ND/ retardo ND, n(%)	24 (26)	19 (28)	58 (45)	33 (47)	0.002
Cualquier deterioro ND/ retardo, n(%)	9 (14)	6 (12)	16 (23)	14 (30)	0.079
Puntuación Integrada Lenguaje, media +/- DE	86±16	87±13	84±17	83±18	0.531
Puntuación Integrada Cognitiva, media +/- DE	91±14	90±10	86±17	88±17	0.33
Puntuación Integrada Motora, media +/- DE	89±15	89±12	86±17	86±18	0.53
Puntuación Integrada lenguaje <70, n (%)	8 (12)	2 (4)	13 (19)	9 (19)	0.081
Puntuación integrada Cognitiva < 70, n (%)	5 (8)	1 (2)	11 (16)	7 (15)	0.0554
Puntuación integrada Motora < 70, n (%)	7 (11)	4 (8)	10 (14)	10 (21)	0.162
Nivel GMFCS >2, n (%)	4 (6)	4 (8)	9 (13)	8 (17)	0.251
Ceguera, n (%)	1 (2)	0	0	0	0.697†
Sordera, n (%)	1 (2)	1 (2)	1 (1)	3 (6)	0.426†

* Niños con evaluación neurológica a los 18-22 ms de edad corregida
† Prueba de Fisher
TA= tensión arterial GMFCS= Sistema de Clasificación de la Motricidad Gruesa, ND= Neurodesarrollo.

Tabla 3 Resultados de la estimación de modelos de regresión logística con un efecto aleatorio

	NIDD		Muerte / NIDD	
Covarianza	O	95% CI	O	95% CI
Cada aumento de 1 semana en la edad gestacional al nacer	0.688	0.479 a 0.988	0.608	0,476 a 0,777
Presencia de algún indicador de gravedad de enfermedad	2.733	1.123 a 6.652	1.872	1,074-3,261
Mayor número acumulado de indicador de gravedad	2.065	1.275 a 3.346	1.672	1,204-2,322
Terapia Antihipotensora	1.53	0.708 a 3.307	1.836	1,092-3,086
Aumento esperado de la TA	0.71	0.347 a 1.454	0.904	0,548-1,493

*Una puntuación de Apgar <3 al min, Hcto <30%, pH < 7,10 en las primeras 24 hs, hemocultivo positivo primeras 72 hs, compresiones torácicas en Sala de Partos.
TA= Tensión arterial, NIDD= deterioro neurológico o retraso en el desarrollo.

Fortalezas de este estudio incluyen datos prospectivos consistentes recolectados por personal de investigación entrenado, inclusión de una extensa población multicéntrica de infantes extremadamente prematuros, análisis basado en la EG en vez del peso de nacimiento y sistemática evaluación del neurodesarrollo por examinadores que desconocían el manejo de la PS temprana del niño y entrenados en la administración estándar de la Escala Bayley de Desarrollo Infantil, Tercera edición. Importante, este estudio puede no haber tenido la potencia

para demostrar diferencias en algunos resultados de los infantes estadísticamente significativos pero de relevancia clínica. Limitaciones adicionales del estudio, reportadas anteriormente, incluyen el diseño observacional, falta de datos acerca de algunas variables que pueden haber contribuido a las decisiones de manejo de la PS, variabilidad en el enrolamiento entre los diferentes centros de NRN y la inconsistencia en cómo fueron obtenidos los valores de PS (14). Hubo sustancial heterogeneidad en el tratamiento de la baja PS percibida, y esto también puede limitar la aplicabilidad de los hallazgos del estudio.

CONCLUSIONES

Los infantes extremadamente prematuros que recibieron tratamiento antihipotensor en las primeras 24 horas de vida tuvieron una tasa significativamente mayor de muerte o déficit del neurodesarrollo a los 18-22 meses de EC que los niños no tratados independiente de los cambios tempranos en la PS. Estos resultados no pueden ser explicados por diferencias en los marcadores de severidad de la enfermedad recabados en este estudio, que incluye factores conocidos de impacto en la sobrevida y la morbilidad. Hay limitada evidencia para sugerir que los tratamientos antihipotensores mejoran los resultados en niños pretérmino, y creciente preocupación acerca de que estos tratamientos pueden ser dañinos. Es posible que las intervenciones terapéuticas para la percepción de baja PS aumenten el riesgo de resultados adversos en los infantes extremadamente pretérmino.

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Early blood pressure, antihypotensive therapy and outcomes at 18–22 months' corrected age in extremely preterm infants

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ABSTRACT

Objective To investigate the relationships between early blood pressure (BP) changes, receipt of antihypotensive therapy and 18–22 months' corrected age (CA) outcomes for extremely preterm infants.

Design Prospective observational study of infants $23^{0/7}$–$26^{6/7}$ weeks' gestational age (GA). Hourly BP values and antihypotensive therapy exposure in the first 24 h were recorded. Four groups were defined: infants who did or did not receive antihypotensive therapy in whom BP did or did not rise at the expected rate (defined as an increase in the mean arterial BP of ≥5 mm Hg/day). Random-intercept logistic modelling controlling for centre clustering, GA and illness severity was used to investigate the relationship between BP, antihypotensive therapies and infant outcomes.

Setting Sixteen academic centres of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network.

Main outcome measures Death or neurodevelopmental impairment/developmental delay (NIDD) at 18–22 months' CA.

Results Of 367 infants, 203 (55%) received an antihypotensive therapy, 272 (74%) survived to discharge and 331 (90%) had a known outcome at 18–22 months' CA. With logistic regression, there was an increased risk of death/NIDD with antihypotensive therapy versus no treatment (OR 1.836, 95% CI 1.092 to 3.086), but not NIDD alone (OR 1.53, 95% CI 0.708 to 3.307).

Conclusions Independent of early BP changes, antihypotensive therapy exposure was associated with an increased risk of death/NIDD at 18–22 months' CA when controlling for risk factors known to affect survival and neurodevelopment.

Clinical trial registration number clinicaltrials.gov #NCT00874393.

What is already known on this topic

- Extremely preterm infants who receive antihypotensive therapies have worse inhospital outcomes.
- The relationship between toddler age outcomes, early blood pressure values and antihypotensive therapies is unclear.
- Investigating these relationships is challenging in part because of changes in blood pressure values occurring shortly after birth.

What this study adds

- Infants given antihypotensive therapy were more likely to have impaired or delayed development than untreated infants irrespective of whether blood pressure increased.
- These results cannot be explained by differences in the markers of severity of illness investigated.

INTRODUCTION

Many investigations in the last 25 years suggest preterm infants considered hypotensive in the immediate postnatal period are at increased risk for adverse outcomes.[1–14] This observation has led some clinicians to administer therapies in an effort to raise arterial blood pressure (BP) and, presumably, improve an infant's chances of survival without major morbidity.[12–16] To date, no such improvement in outcomes has been observed.[1–16] More concerning is the possibility that commonly prescribed antihypotensive therapies may increase risks to preterm infants.[3 7 12–14]

The evolving physiology of extremely preterm infants and the dynamic nature of the cardiovascular system are some of the inherent challenges to investigating BP management in the immediate newborn period. The wide range of BP values observed at any given postnatal hour and the spontaneous rise in BP which typically occurs after birth[5 8 9] make it difficult to determine whether a BP value for a given infant at a specific postnatal age is too high, too low, rising too quickly or not increasing quickly enough. There are no placebo-controlled randomised trials to guide therapeutic decisions.[3 17–19] As such, BP management for this population varies considerably with a wide range in the frequency of antihypotensive therapy administration for perceived low BP.[12–14 16]

Data on the relationship between early BP management and neurodevelopmental impairment/

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developmental delay (NIDD) are insufficient and difficult to interpret. This is related in part to the limited number of studies reporting rates of NIDD, patient sample sizes, data on specific antihypotensive therapies and heterogeneous study populations.[9–11] Perhaps most importantly, previous investigations did not account for the spontaneous rise in BP that occurs after birth in preterm infants.[5 8 9] As a result, it is difficult to determine whether infant outcomes after the administration of antihypotensive therapies are related to BP increasing in conjunction with therapy. The objectives of this study were to evaluate toddler age outcomes in a cohort of extremely preterm infants divided into groups defined by early changes in BP and receipt of antihypotensive therapy in an effort to clarify: (1) whether adverse outcomes in infants with a concerning BP are related to lack of antihypotensive therapy administration and (2) whether survival and/or intact neurodevelopment in treated infants are related to a rise in BP.

METHODS

This study reports the outcomes at 18–22 months' corrected age (CA) for infants enrolled in a prospective observational study of inborn extremely preterm infants born at $23^{0/7}$–$26^{6/7}$ weeks' gestational age (GA) at 16 academic centres of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) enrolled from 21 July 2010 to 21 January 2011. A detailed description of the patient population, explanation of the informed consent process and inhospital outcomes have been reported previously.[8 14] Briefly, hourly BP measurements (both invasive and non-invasive) and the administration of all antihypotensive therapies in the first 24 h were recorded. Antihypotensive therapy included a fluid bolus (≥10 mL/kg of crystalloid), dopamine, dobutamine, hydrocortisone, epinephrine or any blood product. All treatment decisions were made by the clinical care team. Inborn infants born at 23–26 weeks' GA admitted to the neonatal intensive care unit were included in this study. Infants were excluded if they died in the delivery room, had a major birth defect or had intensive care withheld or withdrawn shortly after birth because the clinical care team felt the situation was hopeless. This study was approved by the institutional review board of each participating centre. At two centres, infants were enrolled after parents signed a study-specific informed consent form. At the remaining 14 centres, this study was incorporated into the ongoing Generic Database (GDB) study of the NRN because all infants in this study qualified for GDB enrolment (on the basis of their GA at birth), and both studies collected deidentified patient information. The institutional review board of some NRN centres allowed for GDB data collection with a waiver of consent.[8]

The primary outcome for this investigation was the incidence of death or NIDD at 18–22 months' CA. NIDD was defined as a Bayley Scales of Infant Development, Third Edition[20] cognitive or motor score <70, cerebral palsy (Gross Motor Function Classification System level >2),[21] hearing impairment requiring hearing aids in both ears or blindness (some or no useful vision in either eye). Secondary outcomes were the rates of any NIDD and individual components of NIDD among infants who survived to 18–22 months' CA. Outcomes were compared among four infant groups defined by the administration of antihypotensive therapy and the rate of rise in BP: (1) infants who did not receive an antihypotensive therapy in whom the BP rose as expected, (2) untreated infants in whom BP did not rise at the expected rate, (3) infants who received an antihypotensive therapy in the first 24 h in whom BP rose as expected and (4) treated infants who did not experience the expected rise in BP. The expected rise in BP was defined a priori as an increase in the mean arterial BP of ≥5 mm Hg from postnatal hour 4 to postnatal hour 24. This definition was chosen because this rate of rise was reported previously for extremely preterm infants, this was the average rate of rise in mean arterial BP for this cohort of infants, the average rate of rise was the same for each week of gestation across this GA range and the average rate of rise for this cohort was the same for infants who did versus did not receive an antihypotensive therapy.[5 8]

Data analysis was performed at the NRN Data Coordinating Center (RTI International, Research Triangle Park, North Carolina, USA). Statistical analysis was performed using SAS V.9.3 software (SAS Institute, Cary, North Carolina, USA). For univariable analysis, χ^2 or Fisher's exact tests were used for comparison of proportions and analysis of variance was used for comparison of means. Logistic regression models that included a random intercept to account for potential centre clustering were estimated for the outcomes of death/NIDD and NIDD (alone). Infant-level covariates of GA at birth and severity of illness were used as covariates in addition to antihypotensive therapy exposure (treated vs untreated) and early changes in BP (expected rate of rise vs less than the expected rate of rise).[14] Severity of illness was defined as the cumulative number of any of the following: a 1 min Apgar score ≤3, presence of early anaemia (an initial haematocrit ≤30%), any pH <7.10 in the first 24 h after birth, a positive early blood culture (drawn within 72 h of birth) or delivery room chest compressions.[14]

RESULTS

There were 367 infants enrolled in the study (figure 1). Of these, 158 infants survived the first 24 h without receiving an antihypotensive therapy, including 91 (58%) in whom the mean arterial BP increased by ≥5 mm Hg and 67 (42%) infants in whom it did not. BP rose as expected for 128 (65%) of the 198 infants who received an antihypotensive therapy. Of the 203 infants who received an antihypotensive therapy, 135 (67%) received a fluid bolus, 102 (50%) received a blood product and 92 (45%), 25 (12%), 18 (9%) and 1 (<1%) received dopamine, hydrocortisone, dobutamine and vasopressin, respectively. Five infants who received an antihypotensive therapy died in the first 24 h. Inhospital variables and outcome data for the four infant cohorts are presented in table 1.

Eighteen to 22 months' CA outcomes (death or neurodevelopmental assessment) were known for 331 (90%) infants. This included 99 infants who died and 232 infants who underwent neurodevelopmental testing. Thirty-six infants were lost to follow-up. There were no significant differences in known inhospital morbidities or therapies between infants lost to follow-up and hospital survivors with known 18–22 months' outcomes. On univariable analysis, death or NIDD was significantly higher in treated infants compared with untreated infants (table 2) irrespective of whether BP rose as expected. The rates of individual components of NIDD varied across the four groups, but these differences did not reach statistical significance (table 2; $p>0.05$ for each).

There were significant differences in the incidence of NIDD or the composite outcome of death/NIDD from random-effects logistic regression models (table 3). For each 1-week increase in GA at birth, both the likelihood of NIDD or death/NIDD decreased. The presence of any marker of severity of illness increased the odds of both NIDD and death/NIDD as did the cumulative number of severity of illness markers. When incorporating these variables and changes in BP into regression

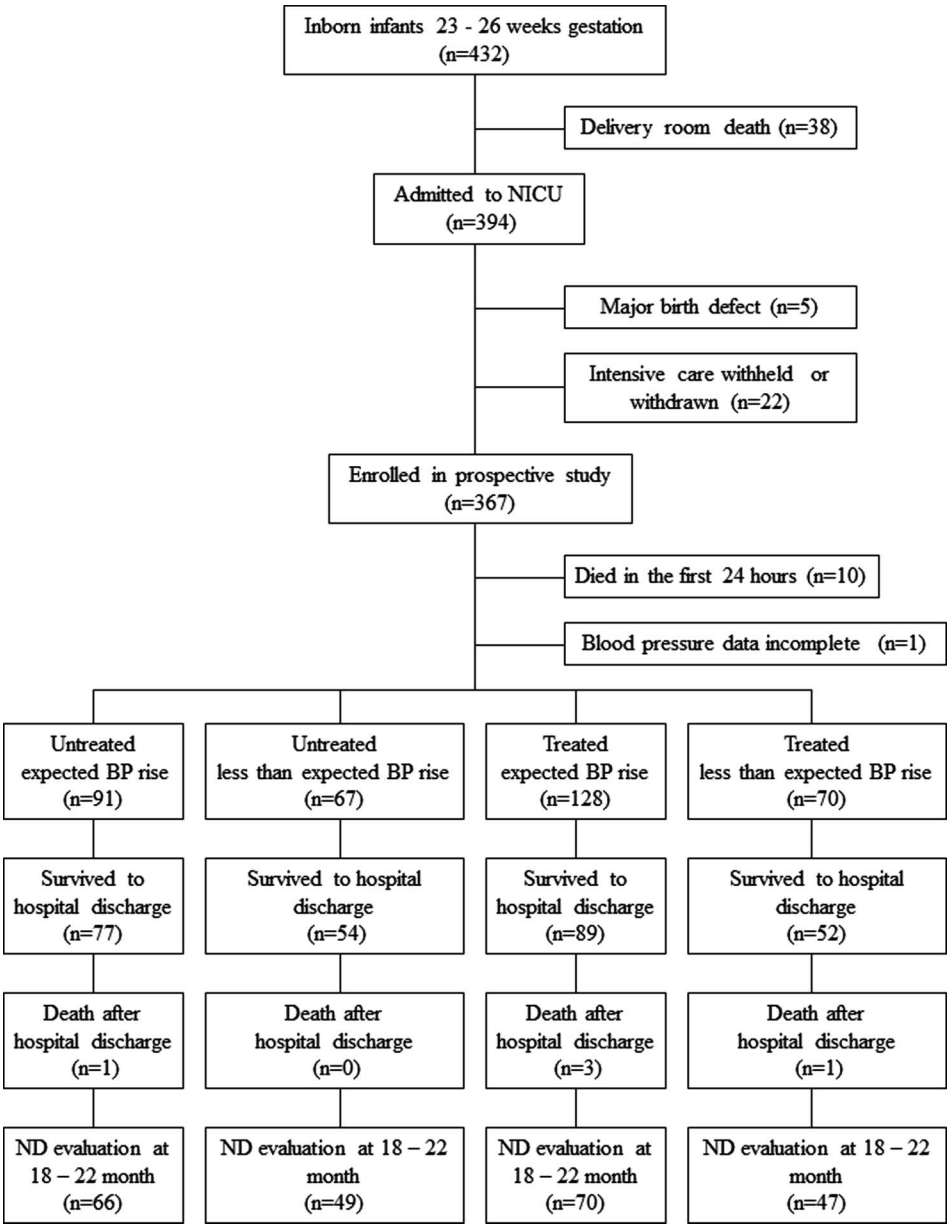

Figure 1 Extremely preterm infant study enrolment classified by study group. BP, blood pressure; ND, neurodevelopmental; NICU, neonatal intensive care unit.

models, treatment with any antihypotensive therapy was a significant predictor of death/NIDD, but not NIDD alone. In similar regression models incorporating antihypotensive treatment, the rise in BP (at the expected rate vs less than the expected rate) was not significantly associated with either outcome.

DISCUSSION

Previous studies examining the relationship between early BP management and infant outcomes either evaluated hypotensive infants versus normotensive infants or infants with treated versus untreated hypotension.[6 9–11] Hypotension was defined as either receipt of an antihypotensive therapy (irrespective of BP values) or a BP value below a numerical threshold (eg, a mean arterial BP less than or equal to the numerical equivalent of the infant's GA), which was not necessarily used clinically. Difficulties with investigating early BP management include the spontaneous rise in BP that occurs after birth, the positive correlation between BP values and GA at birth, and the wide range of BP values observed at any specific postnatal hour for infants at all GA ranges.[5 6 8] The findings of this study underscore the importance of considering multiple factors when examining BP in relation to infant outcomes.

Infants given an antihypotensive therapy had a higher rate of death/NIDD irrespective of early BP changes. The significance of this finding remains unclear. It is possible that the parameters other than a numerical threshold for low BP may better identify infants at risk for a poor outcome who would benefit from therapy. Incorporation of indirect measures of systemic or cerebral blood flow may also partially explain the observed variability in BP management, including why some infants without low BP received an antihypotensive therapy while other infants with low BP did not.[3 14 22 23]

Although not statistically significant (p=0.055), there was a trend towards higher mortality in treated infants (29%) versus untreated infants (17%) in this study, irrespective of the rate of rise in BP. Other reports have also suggested that infants who receive an antihypotensive therapy have a higher mortality rate.[5–7 24] Definitive conclusions regarding this association cannot be made since to date, there are no randomised trials.

Table 1 Inhospital variables and outcomes for infants based on receipt of antihypotensive therapy and rise in blood pressure

	Untreated expected BP rise (n=91)	Untreated less than expected BP rise (n=67)	Treated expected BP rise (n=128)	Treated less than expected BP rise (n=70)	p Value
Birth weight (g), mean±SD	784±165	750±144	692±150	713±168	<0.001
GA at birth (weeks), mean±SD	25.5±0.9	25.6±1.0	25.1±1.1	25.3±1.0	<0.001
Antenatal corticosteroids, n (%)	81 (89)	61 (91)	118 (92)	65 (93)	0.814
Any severity of illness marker, n (%)	37 (41)	37 (55)	93 (73)	56 (80)	<0.001
1 min Apgar score ≤3	33 (36)	33 (49)	79 (62)	49 (70)	<0.001
DR chest compressions	5 (5)	7 (10)	14 (11)	8 (11)	0.5
Positive initial blood culture	0	0	3 (2)	5 (7)	0.01
Any pH <7.10 in the first 24 h	1 (1)	3 (4)	13 (10)	11 (16)	0.003
First haematocrit <30%	4 (4)	3 (4)	25 (20)	12 (17)	<0.001
Severe IVH or PVL, n (%)	11 (12)	8 (13)	28 (23)	21 (31)	0.008
NEC requiring surgery, n (%)	4 (5)	2 (4)	6 (7)	2 (4)	0.881*
Intervention for ROP, n (%)	9 (12)	6 (11)	18 (20)	14 (27)	0.071
BPD, n (%)	40 (51)	36 (63)	58 (62)	34 (62)	0.402
Survival to hospital discharge	77 (85)	54 (81)	89 (70)	52 (74)	0.055

*Fisher's exact test.
BP, blood pressure; BPD, bronchopulmonary dysplasia; DR, delivery room; GA, gestational age; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Potential confounders include higher illness severity in treated infants, a greater likelihood of a condition known to increase mortality (eg, sepsis), inclusion of infants *in extremis* who received an antihypotensive therapy, but were likely to die irrespective of the degree of therapeutic support provided and omission of other factors that may predispose an infant to both perceived low BP requiring intervention and death (such as a low Apgar score or early acidosis). Attempts were made to control for these concerns in the current study such as excluding infants deemed terminally ill in the first 24 h and incorporating severity of illness into the regression analyses using factors, which both impact BP management and are associated with lower survival.[14]

In a previous multicentre study, the ELGAN Study investigators evaluated the relationship between indicators of hypotension and rates of NIDD at 24 months' CA.[9] Similar to this study, those investigators found little evidence of an association between early BP values and subsequent neurodevelopment. Other studies report similar findings.[10 11 18] The association between antihypotensive therapy and hearing loss reported by Fanaroff *et al*[6] was not observed in this investigation, possibly due to the low rate of deafness overall (<3%).

Data from this study and others demonstrate the complex relationship between early BP management, mortality and neurodevelopment. Death and NIDD are distinct outcomes, and it is likely that circumstances which lead to death are distinct but overlap with factors which lead to brain injury such that these therapies—or factors influencing the decision to administer them—may influence mortality risk differently than they influence the risk of NIDD.[25 26] Alternatively, factors beyond the immediate postnatal period may have more influence on toddler age outcomes thus masking the impact of early BP management on neurodevelopment.[25] Lastly, given the complexity of the immature cardiovascular system, antihypotensive therapies may

Table 2 Outcomes at 18–22 months for infants based on receipt of antihypotensive therapy and rise in BP

	Untreated expected BP rise (n=91)	Untreated less than expected BP rise (n=67)	Treated expected BP rise (n=128)	Treated less than expected BP rise (n=70)	p Value
Death or any ND impairment/delay, n (%)	24 (26)	19 (28)	58 (45)	33 (47)	0.002
Any ND impairment/delay, n (%)*	9 (14)	6 (12)	16 (23)	14 (30)	0.079
Language composite score, mean±SD	86±16	87±13	84±17	83±18	0.531
Cognitive composite score, mean±SD	91±14	90±10	86±17	88±17	0.33
Motor composite score, mean±SD	89±15	89±12	86±17	86±18	0.53
Language composite score <70, n (%)*	8 (12)	2 (4)	13 (19)	9 (19)	0.081
Cognitive composite score <70, n (%)*	5 (8)	1 (2)	11 (16)	7 (15)	0.0554
Motor composite score <70, n (%)*	7 (11)	4 (8)	10 (14)	10 (21)	0.162
GMFCS level ≥2, n (%)*	4 (6)	4 (8)	9 (13)	8 (17)	0.251
Blindness, n (%)*	1 (2)	0	0	0	0.697†
Deafness, n (%)*	1 (2)	1 (2)	1 (1)	3 (6)	0.426†

*Denominator is infants who had a neurodevelopmental assessment at 18–22 months' corrected age.
†Fisher's exact test.
BP, blood pressure; GMFCS, Gross Motor Function Classification System; ND, neurodevelopment.

Table 3 Estimation results from logistic regression models with a random intercept

	NIDD		Death/NIDD	
Covariate	**OR**	**95% CI**	**OR**	**95% CI**
Each 1-week increase in GA at birth	0.688	0.479 to 0.988	0.608	0.476 to 0.777
Presence of any marker of severity of illness*	2.733	1.123 to 6.652	1.872	1.074 to 3.261
Higher cumulative number of severity of illness markers	2.065	1.275 to 3.346	1.672	1.204 to 2.322
Any antihypotensive therapy treatment	1.53	0.708 to 3.307	1.836	1.092 to 3.086
Expected BP rise (vs less than the expected rate)	0.71	0.347 to 1.454	0.904	0.548 to 1.493

*One-minute Apgar score ≤3, initial haematocrit ≤30%, any pH <7.10 in the first 24 h, a positive blood culture drawn within 72 h of birth or delivery room chest compressions.
BP, blood pressure; GA, gestational age; NIDD, neurodevelopmental impairment or developmental delay.

inconsistently influence cardiac function such that they do not uniformly alter early postnatal cerebrovascular blood flow or oxygen delivery.[18 22 23]

Study strengths include consistent prospective data collected by trained research personnel, inclusion of a large multicentre population of extremely preterm infants, analysis based on GA rather than birth weight and systematic assessment of neurodevelopment by examiners masked to the infant's early BP management who were trained in the standardised administration of the Bayley Scales of Infant Development, Third Edition. Importantly, this study may have been underpowered to demonstrate statistically significant, but clinically relevant, differences in some infant outcomes. Additional study limitations reported previously include the observational study design, a lack of data for some variables that may have contributed to BP management decisions, variability in infant enrolment across NRN centres and inconsistency in how BP values were obtained.[14] There was substantial heterogeneity in the treatment of perceived low BP, and this also may limit the applicability of the study findings.

CONCLUSIONS

Extremely preterm infants who received an antihypotensive therapy in the first 24 h after birth had a significantly higher rate of death or impaired neurodevelopment at 18–22 months' CA than untreated infants irrespective of early changes in BP. These results cannot be explained by differences in the markers of illness severity collected for this study, which include factors known to impact infant survival and morbidity. There is limited evidence to suggest that antihypotensive therapies improve outcomes for preterm infants, and growing concern that these therapies may be harmful. It is possible that therapeutic interventions for perceived low BP increase the risk of adverse outcomes in extremely preterm infants.

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Early blood pressure, antihypotensive therapy and outcomes at 18–22 months' corrected age in extremely preterm infants

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