RESULTADOS EN NIÑOS NACIDOS <32 SEMANAS DE GESTACIÓN EN UN SOLO CENTRO NEONATAL NIVEL III- RELACIÓN CON LA ESTRATEGIA DE ALIMENTACIÓN

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Resumen

Objetivo: Este estudio quiso determinar sobrevida, morbilidad neonatal, y resultados a 1 y 2 años en niños que nacieron muy PT, y analizar cualquier relación con la alimentación enteral.
Métodos: Llevamos adelante un estudio prospectivo, observacional en infantes MPT (rango 23-31 semanas de EG) nacidos en el Hospital Médico de la Universidad de Innsbruck, Austria entre 2007 y 2014 (n= 557).
Resultados: La tasa general de sobrevida fue 94.6%. Las tasas de sobrevida fueron 77.8%, 78.6%, 90.9%, y 90.9% entre aquellos nacidos a las 24, 25, 26, y 27 semanas, y 97.3 %, 95.3%, 98.3%, y 100% entre aquellos nacidos a las 28, 29, 30, y 31 semanas de gestación, respectivamente. La prevalencia general de enfermedad pulmonar crónica entre los sobrevivientes fue 7.3%. La prevalencia de ECN requiriendo cirugía, hemorragia intraventricular grados 3 y 4, y retinopatía severa de la prematurez fue 3.1%, 2.1%, y 6.2%, respectivamente. No hubo diferencia en la morbilidad a corto plazo o resultado del neurodesarrollo al año o 2 años de edad corregida entre infantes que fueron alimentados con leche humana al alta y aquéllos alimentados con fórmula.
Conclusión: En el presente estudio, las tasas de mortalidad y morbilidad a corto plazo fueron bajas. No se detectaron diferencias en cuanto a la estrategia de alimentación.

Palabras clave: Infante pretérmino, sobrevida, resultado, leche humana, estrategia de alimentación enteral, neurodesarrollo, pequeño para edad gestacional

Introducción

El número de neonatos sobreviviendo al nacimiento MPT ha aumentado gradualmente debido a avances en el cuidado neonatal y perinatal. Sin embargo, la creciente sobrevida está asociada con creciente preocupación acerca de los resultados en morbilidades en estos niños.
La mayoría de los grandes estudios de cohorte que reportaron el resultado de niños nacidos MPT enfocaron exclusivamente en mortalidad y morbilidad a corto plazo de aquéllos nacidos antes de 27 semanas de EG (1, 2). Pese a que los niños que han nacido entre las semanas 27 y 31 de gestación tienen un riesgo relativo menor de resultados adversos, ellos abarcan una proporción mucho más grande de nacimientos prematuros, y en números absolutos, dan cuenta de la mayoría de los niños con déficits (3). Por lo tanto, información actualizada y confiable de base poblacional sobre el resultado incluyendo el grupo MPT es de especial importancia para los cuidadores.
El uso de LH comparada con FPT en infantes MPT (<32 sem EG) durante la hospitalización está asociado con morbilidad intra-hospitalaria reducida. Esta morbilidad incluye tasas más bajas de ECN (4, 6), EPOC, y ROP severa (6), así como

mejores resultados del neurodesarrollo (7, 8). Por tanto, el efecto de la estrategia de alimentación durante la estadía hospitalaria debería ser considerado en los análisis de resultados.
Por tal motivo, este estudió apuntó a reportar las tasas de sobrevida sin morbilidad a corto plazo en todos los infantes nacidos vivos en un área definida geográficamente. También incluimos datos de resultados en neurodesarrollo al año y 2 años de edad y enfocamos en el efecto de la estrategia alimentaria sobre los resultados.

Métodos

Participantes

El área de la investigación fue Tirol, que es un estado en el oeste de Austria con 750 000 habitantes y aproximadamente 7500 nacidos vivos por año. Todos los infantes que nacieron antes de las 32 semanas completas de gestación en el Hospital Universitario de Innsbruck, que es la única UCIN en la región geográfica, fueron enrolados. El período de estudio fue entre Enero de 2007 y Diciembre de 2014.
El estudio de seguimiento fue aprobado por el Comité de Ética de la Universidad Médica de Innsbruck (Nº. AN2013-0086 333/4.2). No fue requerido consentimiento informado de los participantes porque las bases de datos contenían datos de rutina.

Datos Maternos y Neonatales

Los siguientes datos clínicos fueron recogidos prospectivamente: datos maternos y neonatales, incluyendo edad materna, años de educación materna, tabaquismo durante la gestación, uso de esteroides antenatales, EG (semanas completas de gestación), PN (g), PEG, nacimientos múltiples, sexo, uso postnatal de surfactante, diagnóstico de sepsis precoz y tardía, EPOC, hemorragia intraventricular (HIV), ECN, y ROP severa. EG fue calculada desde el primer día del último período menstrual. Esto se comparó con la determinación de EG por ultrasonido que fueron hechos antes de las 24 semanas. Si había una diferencia de más de 1 semana entre la determinación menstrual y el ultrasonido, se prefirió el US. Se emplearon las tablas de crecimiento desarrolladas por Fenton y otros (9) para clasificar los infantes como PEG al nacer. PEG se definió como PN inferior al percentilo 10 para sexo y EG. La mortalidad general se definió como todas las muertes ocurridas después del nacimiento e incluyó la muerte en sala de partos y en UCIN. Los datos sobre tabaquismo durante el embarazo (sí/no) fueron basados en datos auto-reportados. Todos los datos están disponibles para quien los solicite.

Resultados a corto plazo

Se analizaron las siguientes morbilidades mayores a corto plazo. EPOC moderada/ severa se definió como oxígeno- dependencia a las 36 semanas postmenstruales. ECN fue definida según los criterios de Bell (10) y clasificada como médica (síntomas y signos clínicos más evidencia de neumatosis en Rx abdominal) o quirúrgica (evidencia histológica de ECN en muestras quirúrgicas de intestino). HIV se clasificó acorde al método de Papille y otros (11). LPV fue definida por hallazgos ecográficos que sugirieran degeneración de la sustancia blanca periventricular. ROP fue graduada acorde a la clasificación internacional (12). Un diagnóstico de sepsis temprana (≤ 72

después de nacer) o tardía (> 72 hrs) requirió signos de infección generalizada, un cultivo de sangre positivo, y terapia antibiótica por 5 o más días.

Un resultado adverso a corto plazo fue definido como EPOC moderado/severo, ECN con tratamiento quirúrgico, HIV grados 3-4, y ROP grado 3-5.

Resultado a largo plazo

El resultado en neurodesarrollo fue evaluado al año y a los dos años de edad corregida. Fue determinado por exámenes neurológicos y la Escala Bayley-II (13), para niños nacidos entre 2007 y 2013, y Bayley-III (14) para infantes nacidos en 2014. Los scores de Bayley-II proveen índices psicomotor (PDI) y mental (MDI), Bayley III scores de compuesto motor, y desarrollo mental (promedio de los componentes cognitivo y lenguaje). El score medio es 100, y un score de <85 (> de 1 DS por debajo de la media) y ≥ 70 (≤ 2 DS por debajo de la media) indican un desvío y un score <70 (> 2 DS debajo de la media) indican desarrollo anormal. Resultado demorado en ND se definió como score <85 y ≥ 70. Neurodesarrollo anormal se definió como score <70 en el PDI o el MDI en Bayley-II o en el score motor o del desarrollo mental del Bayley-III. Parálisis cerebral (PC) fue clasificada según GMFC (15). Los pacientes con PC (grados 2-5) fueron incluídos en el grupo de infantes con un resultado anormal. Ningún niño tuvo ceguera o pérdida auditiva sensorio-neural que requiriera audífono.
Todos los test cognitivos fueron realizados por uno o dos psicólogos expertos.
Régimen de alimentación enteral

La alimentación enteral comenzó en todos los niños en su primer día de vida. En los neonatos con PN <1000 g, sólo se utilizó LH de la madre o de donante en las primeras cuatro semanas de vida. Un fortificador de leche humana fue agregado al llegar al volumen de 100 ml/kg (Prolacta +4; Prolacta Bioscience Inc., City of Industry, CA, USA). Luego, leche materna (si disponible) y un fortificador bovino o fórmula infantil. En niños con PN entre 1000 g y 1500 g, la leche materna o de donante se utilizó si estaba disponible. Un fortificador bovino fue agregado al llegar a un volumen total de alimentación de 100 ml/kg. Los infantes que pesaron más de 1500 g recibieron leche de su madre, si disponible, o fórmula y un fortificador bovino para un volumen total de 100 ml/kg. El volumen total de alimentación fue incrementado en 10 a 20 ml/kg/día dependiendo del examen físico del estómago, eliminación de meconio, y residuo gástrico.
Los dos grupos de alimentación fueron clasificados en algo de leche humana (LH con fortificador o fórmula) o fórmula (fórmula solamente) basado en la alimentación de las 24 hrs previas al egreso hospitalario. Los datos de alimentación antes del egreso fueron tomados retrospectivamente sede los registros de los pacientes.

Análisis estadístico

El análisis de datos se realizó con programa SPSS, versión 20.0, para Windows (IBM Corp., Armonk, NY, USA). Los datos categóricos fueron comparados utilizando chi-cuadrado o test exacto de Fisher. Los perfiles de riesgo multivariado acorde a la estrategia alimentaria al egreso hospitalario fueron computados por medio de análisis

de regresión logística. El modelo multivariado fue ajustado por edad materna, fumar durante el embarazo, esteroides antenatales, EG, PN, PEG, y sepsis tardía.

Resultados

Durante el período en estudio, hubo 557 nacidos vivos, de los cuales 30 niños murieron. De los restantes 527 niños, 457 (87.1%) y 442 (83.9%) asistieron a las visitas de seguimiento al año y los 2 años de edad. No hubo diferencias significativas en edad materna, uso de esteroides antenatales, EG, PN, sexo, PEG, sepsis precoz y tardía, EPOC, HIV severa, LPV, ROP, y ECN entre los no-participantes y los participantes. El tabaquismo durante la gestación fue significativamente más prevalente en los no-participantes ($p<0.001$) mientras que el surfactante fue más frecuentemente usado en los participantes que en los no-participantes ($p= 0.006$).

La Tabla 1 muestra datos maternos y pre-, peri-, y neonatales para la población de niños que nacieron MPT según el grupo de alimentación al egreso del hospital.

El grupo con fórmula tuvo prevalencia significativamente más alta de baja edad materna (<23 años) ($p=0.001$), baja educación materna (<12 años) ($p=0.032$), tabaquismo durante el embarazo ($p= 0.027$), PEG ($p= 0.002$), y ROP grado 3 y 4 ($p= 0.001$), mientras que el uso de esteroides antenatales fue significativamente menor ($p= 0.005$) que en el grupo con LH. La media de EG y PN fueron significativamente más bajas en el grupo con fórmula que en el grupo con LH (ambas $p< 0.001$). No hubo diferencias significativas en cuanto a todas las otras variables maternas y pre-, peri-, y post- natales entre ambos grupos.

Tabla I. Características neonatales y sociodemográficas de recien nacidos prematuros menores de 32 semanas relacionadas con la estrategia de alimentación al alta.

Variable	Lactancia Materna Exclusiva (n = 429), n (%) o media ± SD	Fórmula (n = 98), n (%) o media ± SD	p valor
Edad materna < 23 años	28 (6.5)	17 (17.3)	0.001
Bajo nivel educativo de la madre (<12 años)	162 (45.5)	47 (58.8)	0.032
Fumadora durante el embarazo	98 (23.0)	33 (33.7)	0.027
Nacimiento múltiple	163 (38.8)	35 (35.7)	0.570
Esteroides antenatales	389 (92.0)	80 (82.5)	0.005
Edad Gestacional (semanas)	29.1 ±1.9	28.2 ± 2.0	<0.001
Peso al nacer (grs)	1304 ± 391	1032 ± 313	<0.001
Pequeño para edad gestacional (PEG)	54 (12.7)	26 (26.5)	0.002
Sexo masculino	229 (53.4)	43 (43.9)	0.089
Tratamiento con Surfactante	233 (55.2)	60 (61.2)	0.280
Enfermedad Pulmonar Crónica	29 (6.8)	9 (9.2)	0.421
Hemorragia Intaventricular (todos los grados)	55 (13.0)	13 (13.3)	0.938
Hemorragia Intraventricular (grados 3-4)	7 (1.7)	4 (4.1)	0.133
Leucomalacia Periventricular	14 (3.3)	2 (2.0)	0.748
Enterocolitis Necrotizante	14 (3.4)	6 (6.3)	0.237
Retinopatía de la Prematuridad (grados 3-4)	19 (4.6)	13 (13.3)	0.001
Sepsis Neonatal Precoz	12 (2.8)	1 (1.0)	0.301
Sepsis Neonatal Tardía	25 (5.9)	8 (8.2)	0.394

Desviación Estandar. Los valores de p fueron obtenidos por test exacto de Fisher o t test. Para todas las variables, excepto el nivel educacional de a madre, la proporción de datos perdidos fue < 5%. La proporción de datos perdidos fue la siguiente: 0.2% para edad materna < 23 años; 17.3% para bajo nivel educativo de la madre; 0.4% para fumadora durante el embarazo; 1.7% para nacimiento múltiple; 1.3% para esteroides antenatales; 1.3% para tratamiento con surfactante; 0.9% para enfermedad pulmonar crónica, hemorragia intraventricular y leucomalacia periventricular; 2.8% para Enterocolitis Necrotizante; 2.5% para ROP; 0.8% para Sepsisi Neonatal temprana y 1.3 para Sepsis Neonatal tardía. No hubo datos perdidos para edad gestacional, peso al nacer, sexo y pequeño para la edad gestacional.

Sobrevida

La tasa general de sobrevida de todos los infantes en las guardias neonatales fue 94.6%. Las tasas de sobrevida en infantes que nacieron a as 23, 24, 25, 26, 27, y 28 semanas de gestación fueron 20.0%, 77.8%, 78.6%, 90.9%, 90.9%, y 97. ·3%, respectivamente. Las tasas de sobrevida fueron 95.3% y 98.3% en aquellos nacidos a las 29 y 30 semanas de gestación. Todos los niños que nacieron a las 31 semanas de gestación, sobrevivieron. No hubo diferencia significativa en la tasa de sobrevida en el período de 8 años del estudio.

Morbilidad a corto plazo

La prevalencia de EPOC, ECN requiriendo cirugía; HIV grados 3 y 4, LPV, y ROP severa fue 7.3%, 3.1%, 2.1%, 3.1%, y 6.2%, respectivamente. La tasa general de ECN fue 3.9%. La sobrevida general libre de un resultado adverso a corto plazo fue 86.5%. Las tasas de resultados adversos a corto plazo de acuerdo a los dos grupos de alimentación se muestran en la Tabla 1.

La alimentación con fórmula al momento del alta hospitalaria estuvo relacionada con un riesgo aumentado de resultado adverso a corto plazo (p= 0.002). Sin embargo, en el modelo multivariado después de ajustar por edad materna al nacer, tabaquismo

durante la gestación, esteroides antenatales, EG al nacer, PN, PEG, y sepsis tardía, esta significancia se perdió (Tabla 2). Cuando enfocamos separadamente en niños con diferentes edades gestacionales (23-26 sem, n= 77; 27-29 sem, n= 113; y 30-31 sem, n=337) tampoco hubo asociación estadísticamente significativa entre la estrategia de alimentación al alta y la morbilidad a corto plazo después de ajustar por las variables arriba mencionadas.

Tabla 2. Asociacion múltiples variables entre allimentación con fórmula al alta y y resultados adversos.

Variable	Sin ajustar OR (95% CI)	p value	Ajustado OR (95% CI)	p value
Resultado adverso a corto plazo	2.40 (1.36–4.24)	0.002	1.08 (0.53–2.21)	0.825
Resultado retrasado a l año	1.03 (0.59–1.80)	0.918	0.88 (0.48–1.64)	0.696
Resultado anormal a l año	1.12 (0.46–2.69)	0.807	0.63 (0.23–1.78)	0.388
Resultado retrasado aa los 2 años	1.52 (0.78–2.96)	0.217	1.22 (0.59–2.51)	0.600
Resultado anormal a los 2 años	2.05 (0.96–4.37)	0.064	1.75 (0.73–4.17)	0.207

Resultado adverso a corto plazo: enfermedad pulmonar crónica moderad/severa. ECN que requiere tratamiento quirúrgico, HIV grado 3 o 4, ROP grado 3 a 5; Resultado retrasado: Indice de desarrollo psicomotor Bayley-II (PDI) y/o Indice de desarrollo mental (MDI) >= 70 y < 85 o puntuación motora compuesta Bayley III y/o puntuación de desarrollo mental (promedio de puntuación compuesta lenguaje - cognitivo) >=70 y < 85; Resultado anormal: Bayley II PDI y/o MDI < 70 o Bayley III < 70 . pacientes con PCI (grasos 2-5) se incluyeron en el grupo de resultado anormal.

Morbilidad a largo plazo

Los resultados del neurodesarrollo a las edades corregidas de 1 y 2 años se muestran en las Tablas 2, 3ª, y 3b. El examen completo de habilidades motoras y cognitivas a 1 año de edad corregida estuvo disponible en 459 (87.1%) de 527 niños. Un total de 247 (66.0%) niños en el grupo de leche humana y 57 (67.1%) en el grupo fórmula lograron scores de Bayley normales en los índices de desarrollo motor y mental (rango: 85-115). En este momento, no hubo diferencias significativas en retraso del desarrollo (escalas de Bayley ≥ 70 y < 85) y desarrollo anormal (Bayley < 70) entre los grupos leche humana y fórmula. A la edad corregida de 2 años, 442 (83.9%) de los 527 niños fueron examinados. Un total de 280 (77.3%) niños en el grupo leche humana y 55 (68.8%) en el grupo fórmula lograron resultado del desarrollo normal en los scores mental y motor. Hubo una tendencia hacia un mejor resultado a los 2 años de edad en el grupo leche humana comparado con el grupo fórmula, pero esta no fue significativa. No hubo diferencias significativas en el resultado a largo plazo cuando enfocamos separadamente en las diferentes EGs (23-26 sem, 27-29 sem, y 30-31 semanas) entre los grupos de alimentación.

Tabla 3a. Resultados del Neurodesarrollo al año de edad corregida en recien nacidos menores de 32 semanas de acuerdo a la estarategia de alimentación al alta.

Variable	Lactancia materna exclusiva (n = 374), n (%)	Fórmula (n = 85), n (%)
Resultado retrasado	97 (25.9)	21 (24.7)
Resultado anormal	30 (8.0)	7 (8.2)

Tabla 3b. Resultados del Neurodesarrollo a los 2 años de edad corregida en recién nacidos menores de 32 sem relacionado con la estategia de alimentación al alta.

Variable	Lactancia Materna Exclusiva (n = 362), n (%)	Fórmula (n = 80), n (%)
Resultado retrasado	52 (14.4)	14 (17.5)
Resultado Anormal	30 (8.3)	11 (13.8)

Resultado retrasado: Indice de desarrollo psicomotor Bayley-II (PDI) y/o Indice de desarrollo mental (MDI) >= 70 y < 85 o puntuación motora compuesta Bayley III y/o puntuación de desarrollo mental (promedio de puntuación compuesta lenguaje cognitivo) >=70 y < 85; Resultado anormal: Bayley II PDI y/o MDI < 70 o Bayley III < 70 .
Pacientes con PCI (grasos 2-5) se incluyeron en el grupo de resultado anormal.

Discusión

La tasa general de sobrevida de todos los nacidos vivos fue 94.6% en esta cohorte de base poblacional de niños nacidos MPT entre 2007 y 2014. Las tasas de sobrevida en el grupo de EPT (nacidos con <28 sem EG) también fueron altas con 77.8% entre aquellos nacidos a las 24 sem EG, y más de 90% en aquellos con EG mayor de 26 semanas. Las tasas de sobrevida de infantes nacidos vivos en los estudios de cohorte de base poblacional varían grandemente, especialmente en cuanto a infantes EPT (1, 16-29),

con tasas que van desde 35% (25, 29) a 70% (1), y desde 59% (29) a 81% (1) para aquellos con 25 sem EG. Las tasas de sobrevida más altas en nuestros niños con EG de 24 semanas o más pueden reflejar avances en el cuidado perinatal y neonatal con elevadas tasas de utilización de corticosteroides antenatales (90.2%) y uso de surfactante (56.3%). Nuestra tasa de sobrevida para este grupo es baja (20%) comparada con la de países con resucitación activa para neonatos nacidos a las 23 semanas de gestación (Suecia). Sin embargo, durante los últimos 3 años, ya cambiamos nuestra práctica a favor de tratamiento proactivo y la futura tasa de sobrevida de estos neonatos muy inmaduros probablemente será más alta.

La tasa general de sobrevida que estuvo libre de un resultado adverso a corto plazo (EPOC moderada/severa, ECN requiriendo cirugía, HIV grados 3-4, y ROP grados 3-5) fue 86.5% en nuestro estudio. La prevalencia general de EPOC moderada/severa, ECN severa, HIV grados 3 a 4, y ROP severa fue 7.3%, 3.1%, 2.1%, y 6.2%, respectivamente. Los resultados en el estudio de cohorte EPIPAGE2 fueron similares a los de nuestro estudio, con una tasa de sobrevida libre de resultado adverso a corto plazo de 82.9% para aquellos nacidos entre las 23 y 31 semanas de gestación (27). Más aún, la prevalencia de EPOC moderada/severa, ECN severa, HIV, y ROP severa fue 8.0%, 3.7%, 5.3%, y 1.2%, respectivamente. Otros estudios que sólo se enfocaron en infantes EPT reportaron frecuencias marcadamente más altas de morbilidades a corto plazo (16, 20, 30). La prevalencia de EPOC severa en otros estudios fue de 25% (30) a 44% (20), y la prevalencia de ROP severa fue desde 8% (16) a 34% (30). La prevalencia más baja de HIV severa en infantes EPT fue 6.0% en un estudio sueco (19), 6.9% en un estudio holandés (16), y 5.3% en otro estudio que incluyó infantes EPT y MPT (27). La incidencia media de NEC fue reportada entre 7% a 10% entre infantes EPT (31). En la cohorte EPIPAGE-2, la tasa de ECN severa fue 3.7% en niños nacidos entre 23 y 31 semanas de gestación (27).

Un total de 335 (75.8%) de 442 niños mostraron desarrollo motor y mental normal a la edad corregida de dos años. Las tasas reportadas de ningún déficit del desarrollo o discapacidad utilizando el examen de Bayley a los dos años de edad en los infantes sobrevivientes varía desde 70.6% en los Países Bajos (16) a 52.1% en Australia (32), y 42% en Suecia (18). Todos estos estudios reportaron resultados de infantes EPT solamente. El estudio de cohorte EPIPAGE-2 reportó un resultado mucho mejor, en el cual 80.5% de todos los niños nacidos entre 23 y 31 semanas de gestación sobrevivieron sin discapacidad neuromotora o sensorial a los dos años de edad corregida (33). Sin embargo, en esta cohorte no se empleó el test de Bayley para definir el resultado. Generalmente, los resultados del desarrollo son difíciles de comparar debido a diferentes métodos de evaluación y diferentes definiciones de discapacidad utilizada.

Nuestro estudio no mostró diferencia en el resultado del neurodesarrollo a1 y 2 años de edad entre el grupo de leche humana y el de fórmula según las pruebas de Bayley-II y Bayley- III. Este resultado puede ser explicado por la alta tasa de amamantamiento de 81.4% al momento del alta hospitalaria. Este hallazgo también puede ser explicado por la estrategia local de alimentación utilizando sólo leche humana en neonatos que pesaron menos de 1000 gramos y leche de madre o de donante si disponible en neonatos que pesaron 100 a 1500 grs. Nuestros resultados concuerdan con un estudio recientemente publicado por O´Connor y otros (34). Estos autores no encontraron mejora en el resultado en infantes MBPN a los 18 meses de edad corregida cuando se

les alimentó con leche de donante en lugar de fórmula como suplemento de la leche materna. Los autores concluyeron que si la leche de donante se utiliza en ámbitos de alta provisión de leche materna, el resultado mejorado del neurodesarrollo no debiera ser considerado como meta del tratamiento.

Las fortalezas de este estudio incluyen el diseño de cohorte de base poblacional con inclusión prospectiva de infantes que fueron no sólo EPT sino también MPT. Estos resultados han sido reportados infrecuentemente. Más aún, el efecto de la alimentación durante la estadía hospitalaria fue incluído en los datos de resultado. Especialistas en pediatría y en neurología pediátrica llevaron a cabo los exámenes de seguimiento y psicólogos certificados administraron las pruebas Bayley-II y Bayley-III.

Una limitación de nuestro estudio es el número de niños que se perdieron para el seguimiento, pese a que las tasas de seguimiento a 1 y 2 años de edad fueron altas con 87.1% y 83.9%, respectivamente. Sin embargo, encontramos un sesgo social en la participación, con más madres que fumaron durante la gestación rechazando participar en el seguimiento. Otra limitación es la edad temprana de seguimiento porque los problemas cognitivos y académicos pueden hacerse evidentes más tarde (35). Adicionalmente, nuestro estudio se enfocó en diferencias de resultado en cuanto a estrategia de alimentación y no fue un trabajo randomizado, controlado. Sin embargo, la randomización entre leche humana y fórmula no hubiera sido posible por razones éticas. Más aún, sólo se calcularon diferencias en resultado entre aquellos alimentados con leche humana (cualquier cantidad) y aquellos alimentados con fórmula al alta. Esto es porque la cantidad precisa de leche humana no pudo ser extraída de los registros de los pacientes retrospectivamente.

Este estudio provee la primera descripción completa de resultado de infantes MPT que nacieron en Tirol. Para comparar estos datos con otras poblaciones, el sistema austríaco de salud y la política de tratamiento de infantes MPT debe ser considerada. El cuidado de la salud en Austria es accesible para toda la población y todos tienen cobertura de seguro de salud. El cuidado perinatal está bien estructurado y es ofrecido a toda mujer embarazada. Este sistema de salud puede llevar a mejor cuidado durante el embarazo y podría también ser una explicación para los buenos datos de resultado en infantes MPT.

Conclusiones

Nuestro estudio de base poblacional de infantes MPT muestra que las tasas de mortalidad y morbilidad a corto plazo son bajas. No hay diferencia en la morbilidad a corto plazo o resultado en neurodesarrollo a 1 o 2 años de edad corregida entre infantes que fueron alimentados con leche humana al alta y aquellos alimentados con fórmula. Los avances en cuidado perinatal y neonatal, así como la alta tasa de alimentación con leche humana durante la estadía hospitalaria, juegan un papel importante en una estrategia exitosa para bajas tasas de complicaciones en estos niños.

Referencias

1. EXPRESS Group, Fellman V, Hellstr€om- Westas L, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009; 301: 2225–2233.

2. Bolisetty S, Dhawan A, Abdel-Latif M, et al. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 2014; 133: 55–62.
3. Larroque B, Ancel PY, Marret S, et al. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. Lancet 2008; 371: 813–820.
4. Schanler RJ, Shulman RJ and Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. Pediatrics 1999; 103: 1150–1157.
5. Schanler RJ, Lau C, Hurst NM, et al. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. Pediatrics 2005; 116: 400–406.
6. Maayan-Metzger A, Avivi S, Schushan- Eisen I, et al. Human milk versus formula feeding among preterm infants: short-term outcomes. Am J Perinatol 2012; 29: 121–126.
7. Vohr BR, Poindexter BB, Dusick AM, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. Pediatrics 2006; 118: e115–e123.
8. Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics 2007; 120: e953–e959.
9. Fenton TR and Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013; 13: 59.
10. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978; 187: 1–7.
11. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. J Pediatr 1978; 92: 529–534.
12. An international classification of retinopathy of prematurity. Committee for the classification of retinopathy of prematurity. Arch Ophthalmol 1984; 102: 1130–1134. (https://www.ncbi.nlm.nih.gov/pubmed/6547831)
13. Bayley N. Bayley scales of infant and toddler development. 2nd ed. San Antonio, TX: Psychological Corporation, 1993.
14. Bayley N. Bayley scales of infant and toddler development. 3rd ed. San Antonio, TX: Harcourt Assessment, 2006.
15. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther 2000; 80: 974–985.
16. de Waal CG, Weisglas-Kuperus N, van Goudoever JB, et al. Mortality, neonatal morbidity and two year follow-up of extremely preterm infants born in The Netherlands in 2007. PLoS One 2012; 7: e41302.
17. Larroque B, Breart G, Kaminski M, et al. Survival of very preterm infants: epipage, a population based cohort study. Arch Dis Child Fetal Neonatal Ed 2004; 89: F139–F144.
18. Serenius F, K€alle´n K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. JAMA 2013; 309: 1810–1820.
19. Markestad T, Kaaresen PI, Rønnestad A, et al. Early death, morbidity, and need of treatment among extremely premature infants. Pediatrics 2005; 115: 1289–1298.
20. Vanhaesebrouck P, Allegaert K, Bottu J, et al. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. Pediatrics 2004; 114: 663–675.
21. Chan K, Ohlsson A, Synnes A, et al. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. Am J Obstet Gynecol 2001; 185: 220–226.
22. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. Pediatrics 2010; 126: 443–456.
23. Costeloe KL, Hennessy EM, Haider S, et al. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 2012; 345: e7976. doi: 10.1136/
bmj.e7976
24. Boland RA, Davis PG, Dawson JA, et al. Predicting death or major neurodevelopmental disability in extremely preterm infants born in Australia. Arch Dis Child Fetal Neonatal Ed 2013; 98: F201–F204. doi: 10.1136/archdischild-2012–301628
25. Berger TM, Steurer MA, Woerner A, et al; Swiss neonatal network. Trends and centreto- centre variability in survival rates of very preterm infants (<32 weeks) over a 10-yearperiod in Switzerland. Arch Dis Child Fetal Neonatal Ed 2012; 97: F323–F328.

26. Younge N, Goldstein RF, Cotten CM, et al. Survival and neurodevelopment of periviable infants. N Engl J Med 2017; 376: 1890–1891. doi: 10.1056/NEJMc1703379
27. Ancel PY, Goffinet F, EPIPAGE-2 Writing Group, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. JAMA Pediatr 2015; 169: 230–238. doi: 10.1001/jamapediatrics.2014.3351
28. Mercier CE, Dunn MS, Ferrelli KR, et al. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998–2003. Neonatology 2010; 97: 329–338. doi: 10.1159/000260136
29. Field DJ, Dorling JS, Manktelow BN, et al. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994–9 compared with 2000–5. BMJ 2008; 336: 1221–1223. doi:
10.1136/bmj.39555.670718.BE
30. EXPRESS Group. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). Acta Paediatr 2010; 99: 978–992. doi: 10.1111/j.1651–2227.2010.
01846.x
31. Thompson AM and Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. Drugs 2008; 68: 1227–1238.
32. Doyle LW, Roberts G, Anderson PJ, et al. Outcomes at age 2 years of infants<28 weeks' gestational age born in Victoria in 2005. J Pediatr 2010; 156: 49–53.e1. doi: 10.1016/j.jpeds.2009.07.013
33. Pierrat V, Marchand-Martin L, Arnaud C, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. BMJ 2017; 358: j3448. doi: 10.1136/bmj.j3448
34. O'Connor DL, Gibbins S, Kiss A, et al. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial. JAMA 2016; 316: 1897–905. doi: 10.1001/jama.2016.16144
35. Aarnoudse-Moens CS, Oosterlaan J, Duivenvoorden HJ, et al. Development of preschool and academic skills in children born very preterm. J Pediatr 2011; 158: 51–56

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Outcome of infants born at < 32 weeks' gestation in a single-centre level III neonatology unit – relation to feeding strategy

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Abstract

Objective: This study aimed to determine survival, neonatal morbidity, and outcomes at 1 and 2 years in children who were born very preterm, and to analyse any relation to enteral feeding.

Methods: We performed a prospective, observational study on very preterm infants (range: 23–31 weeks' gestation) born at Innsbruck Medical University Hospital, Austria, between 2007 and 2014 (n = 557).

Results: The overall survival rate was 94.6%. Survival rates were 77.8%, 78.6%, 90.9%, and 90.9% among those born at 24, 25, 26, and 27 weeks, and 97.3%, 95.3%, 98.3%, and 100% among those born at 28, 29, 30, and 31 weeks of gestation, respectively. The overall prevalence of chronic lung disease among survivors was 7.3%. The prevalence of necrotizing enterocolitis requiring surgery, intraventricular haemorrhage grades 3 and 4, and severe retinopathy of prematurity was 3.1%, 2.1%, and 6.2%, respectively. There was no difference in short-term morbidity or neurodevelopmental outcome at 1 or 2 years of corrected age between infants who were fed with human milk at discharge and those who were formula-fed.

Conclusion: In the current study, mortality and short-term morbidity rates were low. No differences regarding feeding strategy were detected.

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Preterm infant, survival, outcome, human milk, enteral feeding strategy, neurodevelopment, small for gestational age

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Introduction

The number of neonates surviving very preterm birth has gradually increased because of advances in perinatal and neonatal care. However, increasing survival is associated with an increased awareness of morbidity outcomes in these children.

Most of the large cohort studies that reported the outcome of very preterm-born children exclusively focussed on mortality and short-term morbidity of those born before 27 weeks' gestation.[1,2] Even though children who are born between 27 and 31 weeks have a lower relative risk for adverse outcomes, they comprise a much larger proportion of preterm births, and in absolute numbers, they account for most children with deficits.[3] Therefore, up-to-date and reliable population-based information on outcome including the very preterm group is of special importance for caregivers.

The use of human milk compared with preterm infant formula in very preterm infants (born < 32 weeks' gestation) during hospitalization is associated with reduced in-hospital morbidity. This morbidity includes lower rates of necrotizing enterocolitis (NEC),[4–6] chronic lung disease (CLD), and severe retinopathy of prematurity (ROP),[6] as well as improved neurodevelopmental outcomes.[7,8] Therefore, the effect of the enteral feeding strategy during the hospital stay should be considered in analyses of outcome data.

Therefore, this study aimed to report survival rates and survival without short-term morbidity in all live-born very preterm infants in a geographically defined area. We also included data on neurodevelopmental outcomes at 1 and 2 years old and focussed on the effect of feeding strategy on outcome data.

Methods

Participants

The study survey area was Tyrol, which is a state in western Austria with 750,000 inhabitants and approximately 7500 live births per year. All infants who were born before 32 completed weeks of pregnancy at Innsbruck Medical University Hospital, which is the only neonatal intensive care unit in the geographical region, were enroled. The study period was between January 2007 and December 2014.

The follow-up study was approved by the ethics committee of the Medical University of Innsbruck (No. AN2013–0086 333/4.2). Informed consent of the participants was not required because the database only contained routine data.

Maternal and neonatal data

The following clinical data were prospectively collected: maternal and neonatal data, including maternal age, maternal years of education, smoking during pregnancy, antenatal steroid use, gestational age (full weeks of gestation), birth weight (g), small for gestational age (SGA), multiple births, sex, postnatal surfactant use, diagnosis of early- and late-onset sepsis, CLD, intraventricular haemorrhage (IVH),

NEC, and severe ROP. Gestational age was calculated from the first day of the last menstrual period. This was compared with assessment of gestational age by ultrasound scans that were performed before 24 weeks. If there was a difference of more than 1 week between menstrual and ultrasound assessment, assessment of the scan was preferred. Growth charts developed by Fenton et al.[9] were used to classify infants as SGA at birth. SGA was defined as a birth weight lower than the 10th percentile for sex and gestational age. Overall mortality was defined as all deaths that occurred after birth and included delivery room and neonatal intensive care unit deaths. Smoking habits during pregnancy (yes/no) were based on self-reported data. All data are available on request.

Short-term outcome

The following major short-time morbidities were analysed. Moderate/severe CLD was defined as oxygen dependence at 36 weeks' postmenstrual age. NEC was defined according to Bell's criteria[10] and classified as medical (clinical symptoms and signs plus evidence of pneumatosis on an abdominal x-ray) or surgical (histological evidence of NEC on surgical specimens of the intestine). IVH was classified according to the method of Papile et al.[11] Cystic periventricular leukomalacia (PVL) was defined by ultrasonographic findings that suggested cystic degeneration of periventricular white matter. ROP was graded according to international classification.[12] A diagnosis of early-onset (≤ 72 hours after birth) or late-onset (> 72 hours) sepsis required signs of generalized infection, a positive blood culture, and antibiotic therapy for 5 or more days.

An adverse short-term outcome was defined as moderate/severe CLD, NEC requiring surgical treatment, IVH grades 3 to 4, and ROP grades 3 to 5.

Long-term outcome

Neurodevelopmental outcome was assessed at 1 and 2 years of corrected age. Neurodevelopmental outcome was determined by neurological examinations and the Bayley Scales of Infant and Toddler Development, second edition (Bayley-II),[13] for infants born between 2007 and 2013, and the third edition (Bayley-III)[14] for infants born in 2014. Bayley-II scores provide psychomotor (PDI) and mental (MDI) developmental indices, Bayley-III scores motor composite, and mental developmental scores (mean of cognitive and language composite scores). The mean score is 100, and a score of < 85 (>1 standard deviation [SD] below the mean) and ≥ 70 (≤ 2 SDs below the mean) indicates a delay and a score of < 70 (> 2 SDs below the mean) indicates abnormal development. Delayed neurodevelopmental outcome was defined as a score of < 85 and ≥ 70. Abnormal neurodevelopmental outcome was defined as a score of < 70 on either the PDI or the MDI of the Bayley-II or the motor composite or mental developmental score of the Bayley-III. Cerebral palsy was classified by the Gross Motor Function Classification.[15] Patients with cerebral palsy (grades 2–5) were included in the group of infants with an abnormal outcome. No children had blindness or sensorineural hearing loss that required a hearing aid.

All cognitive tests were performed by one of two experienced psychologists.

Enteral feeding regime

Enteral feeding was started in all infants on their first day of life. In neonates with a birth weight of less than 1000 g, only donor human milk or mother's milk was used in the first 4 weeks of life. A human milk fortifier was added at a feeding volume of 100 mL/kg (Prolacta +4; Prolacta Bioscience Inc., City of Industry,

CA, USA). Thereafter, mother's milk (if available) and a bovine fortifier or infant formula were provided. In children with a birth weight between 1000 g and 1500 g, mother's milk or donor human milk if available was used. A bovine fortifier was added at a total feeding volume of 100 mL/kg. Infants who weighed more than 1500 g received mother's milk if available or formula and a bovine fortifier for a total feeding volume of 100 mL/kg. The total feeding volume was increased by 10 to 20 mL/kg/day depending on a physical examination of the stomach, meconium passage, and gastric residuals.

The two feeding groups were classified as any human milk (human milk with either fortifier or formula) or formula (formula only) based on feeding in the previous 24 hours before discharge from hospital. Data on feeding before discharge were retrospectively collected from the patients' records.

Statistical analysis

Data analysis was performed with SPSS software, version 20.0, for Windows (IBM Corp., Armonk, NY, USA). Categorical data were compared using the chi-square or Fisher's exact test. Multivariate risk profiles according to feeding strategy at discharge from hospital were computed by means of logistic regression analysis. The multivariate model was adjusted for maternal age, smoking during pregnancy, antenatal steroids, gestational age, birth weight, SGA, and late-onset sepsis.

Results

During the study period, there were 557 live births, of which 30 children died. Of the remaining 527 children, 459 (87.1%) and 442 (83.9%) attended follow-up visits at 1 and 2 years old. There were no significant differences in maternal age, maternal education, antenatal steroid use, gestational age, birth weight, sex, SGA, early- and late-onset sepsis, CLD, severe IVH, PVL, ROP, and NEC between non-participants and participants. Smoking during pregnancy was significantly more prevalent in non-participants than in participants ($p < 0.001$), whereas surfactant was more frequently used in participants than in non-participants ($p = 0.006$).

Table 1 shows maternal and pre-, peri-, and neonatal data for the population of children who were born very preterm according to the feeding group at discharge from hospital.

The formula group had a significantly higher prevalence of low maternal age (< 23 years) ($p = 0.001$), low maternal education (< 12 years) ($p = 0.032$), smoking during pregnancy ($p = 0.027$), SGA ($p = 0.002$), and ROP grades 3 and 4 ($p = 0.001$), whereas the use of antenatal steroids was significantly lower ($p = 0.005$) than in the human milk group. Mean gestational age and birth weight were significantly lower in the formula group than in the human milk group (both $p < 0.001$). No significant differences were found regarding all other maternal and pre-, peri-, and postnatal variables between these two groups.

Survival

The overall survival rate of all infants in the neonatal wards was 94.6%. Survival rates in infants who were born at 23, 24, 25, 26, 27, and 28 weeks of gestation were 20.0%, 77.8%, 78.6%, 90.9%, 90.9%, and 97.3%, respectively. The survival rates were 95.3% and 98.3% in those born at 29 and 30 weeks of gestation. All of the children who were born at 31 weeks of gestation survived. There was no significant difference in the survival rate over the 8-year study period.

Table 1. Sociodemographic and neonatal characteristics of preterm infants with a gestational age of fewer than 32 weeks according to feeding strategy at discharge from hospital

Variable	Any human milk (n = 429), n (%) or mean ± SD	Formula (n = 98), n (%) or mean ± SD	p value
Maternal age < 23 years	28 (6.5)	17 (17.3)	0.001
Low educational level of the mother (< 12 years)	162 (45.5)	47 (58.8)	0.032
Smoking during pregnancy	98 (23.0)	33 (33.7)	0.027
Multiple births	163 (38.8)	35 (35.7)	0.570
Antenatal steroids	389 (92.0)	80 (82.5)	0.005
Gestational age (weeks)	29.1 ±1.9	28.2 ± 2.0	<0.001
Birth weight (g)	1304 ± 391	1032 ± 313	<0.001
SGA	54 (12.7)	26 (26.5)	0.002
Male sex	229 (53.4)	43 (43.9)	0.089
Surfactant treatment	233 (55.2)	60 (61.2)	0.280
CLD	29 (6.8)	9 (9.2)	0.421
IVH (all grades)	55 (13.0)	13 (13.3)	0.938
IVH (grades 3–4)	7 (1.7)	4 (4.1)	0.133
PVL	14 (3.3)	2 (2.0)	0.748
NEC	14 (3.4)	6 (6.3)	0.237
ROP (grades 3–4)	19 (4.6)	13 (13.3)	0.001
Early-onset sepsis	12 (2.8)	1 (1.0)	0.301
Late-onset sepsis	25 (5.9)	8 (8.2)	0.394

SD: standard deviation; SGA: small for gestational age; CLD: chronic lung disease; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity. The p values were obtained by Fisher's exact test or the t test, as appropriate. For all variables, except for educational level of the mother, the proportion of missing data was < 5%. The proportions of missing data were as follows: 0.2% for maternal age < 23 years; 17.3% for low educational level of the mother; 0.4% for smoking during pregnancy; 1.7% for multiple births; 1.3% for antenatal steroids; 1.3% for surfactant treatment; 0.9% for CLD, IVH, and PVL; 2.8% for NEC; 2.5% for ROP; 0.8% for early-onset sepsis; and 1.3% for late-onset sepsis. There were no missing data for gestational age, birth weight, sex, and SGA.

Short-term morbidity

The prevalence of CLD, NEC requiring surgery, IVH grades 3 and 4, PVL, and severe ROP was 7.3%, 3.1%, 2.1%, 3.1%, and 6.2%, respectively. The overall NEC rate was 3.9%. Overall survival that was free of an adverse short-term outcome was 86.5%. The rates of adverse short-term outcomes according to the two feeding groups are shown in Table 1.

Formula feeding at discharge from hospital was related to an increased risk of adverse short-term outcome ($p = 0.002$). However, in the multivariate model after adjustment for maternal age at birth, smoking during pregnancy, antenatal steroids, gestational age at birth, birth weight, SGA, and late-onset sepsis, this significance was lost (Table 2). When we separately focussed on children with different gestational ages (23–26 weeks, n = 77; 27–29 weeks, n = 113; and 30–31 weeks, n = 337) there was also no significant association between the feeding strategy at discharge and short-term morbidity after adjustment for the above-mentioned variables.

Table 2. Multivariable associations between formula feeding at discharge and adverse outcome

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Adverse short-term outcome	2.40 (1.36–4.24)	0.002	1.08 (0.53–2.21)	0.825
Delayed outcome at 1 year	1.03 (0.59–1.80)	0.918	0.88 (0.48–1.64)	0.696
Abnormal outcome at 1 year	1.12 (0.46–2.69)	0.807	0.63 (0.23–1.78)	0.388
Delayed outcome at 2 years	1.52 (0.78–2.96)	0.217	1.22 (0.59–2.51)	0.600
Abnormal outcome at 2 years	2.05 (0.96–4.37)	0.064	1.75 (0.73–4.17)	0.207

Adverse short-term outcome: moderate/severe CLD, NEC requiring surgical treatment, IVH grades 3 to 4, ROP grades 3 to 5; delayed outcome: Bayley-II psychomotor developmental index (PDI) and/or mental developmental index (MDI) ≥ 70 and < 85 or Bayley-III motor composite score and/or mental developmental score (mean of cognitive and language composite scores) ≥ 70 and < 85; abnormal outcome: Bayley-II PDI and/or MDI < 70 or Bayley-III motor composite score and/or mental developmental score < 70. Patients with cerebral palsy (grades 2–5) were included in the group of infants with an abnormal outcome. CI: confidence interval; OR: odds ratio derived from logistic regression analysis of risk variables for an adverse outcome. The multivariate model was adjusted for maternal age, smoking during pregnancy, antenatal steroids, gestational age, birth weight, small for gestational age, and late-onset sepsis.

Table 3a. Neurodevelopmental outcome at 1 year of corrected age in preterm infants with a gestational age of less than 32 weeks according to feeding strategy at discharge from hospital

Variable	Any human milk (n = 374), n (%)	Formula (n = 85), n (%)
Delayed outcome	97 (25.9)	21 (24.7)
Abnormal outcome	30 (8.0)	7 (8.2)

Table 3b. Neurodevelopmental outcome at 2 years of corrected age in preterm infants with a gestational age of less than 32 weeks according to feeding strategy at discharge from hospital

Variable	Any human milk (n = 362), n (%)	Formula (n = 80), n (%)
Delayed outcome	52 (14.4)	14 (17.5)
Abnormal outcome	30 (8.3)	11 (13.8)

Delayed outcome: Bayley-II psychomotor developmental index (PDI) and/or mental developmental index (MDI) ≥ 70 and < 85 or Bayley-III motor composite score and/or mental developmental score (mean of cognitive and language composite scores) ≥ 70 and < 85; abnormal outcome: Bayley-II PDI and/or MDI < 70 or Bayley-III motor composite score and/or mental developmental score < 70. Patients with cerebral palsy (grades 2–5) were included in the group of infants with an abnormal outcome.

Long-term morbidity

Neurodevelopmental outcomes at corrected ages of 1 and 2 years are shown in Tables 2, 3a, and 3b. Full assessment of motor and cognitive abilities at 1 year of corrected age was available in 459 (87.1%) of the 527 children. A total of 247 (66.0%) children in the human milk group and 57 (67.1%) in the formula group achieved normal Bayley scores in motor and mental developmental indices (range: 85–115). At this time, there were no significant differences in developmental delay (Bayley scales ≥ 70 and < 85) and abnormal development (Bayley score < 70) between the human milk and formula groups. At a corrected age of 2 years, 442 (83.9%) of the 527 children were tested. A total of 280 (77.3%) children in the human milk group and 55 (68.8%) in the formula group achieved a normal developmental outcome in motor and mental scores. There was a trend towards a better outcome at 2 years old in the human milk group compared with the formula group, but this was not significant. There were no significant

differences in long-term outcome when we separately focussed on different gestational ages (23–26 weeks, 27–29 weeks, and 30–31 weeks) between the feeding groups.

Discussion

The overall survival rate of all live-born infants was 94.6% in this population-based cohort of very preterm-born children between 2007 and 2014. Survival rates in the extremely preterm age group (born at < 28 weeks' gestation) were also high at 77.8% among those born at 24 weeks of gestation, and over 90% in those with a gestational age of more than 26 weeks. Survival rates of live-born infants in population-based cohort studies greatly vary, especially regarding extremely preterm infants,[1,16–29] with rates ranging from 35%[25,29] to 70%[1], and from 59%[29] to 81%[1] for those at 25 weeks of gestation. High overall survival rates in our children at a gestational age of 24 weeks or higher may reflect advances in perinatal and neonatal care with high rates of antenatal corticosteroids (90.2%) and surfactant use (56.3%). Our survival rate for this group is low (20%) compared with that in countries with active resuscitation for neonates born at 23 weeks of gestation (Sweden). However, during the last 3 years, we already changed our practice in favour of proactive treatment and the future survival rate of these very immature neonates will probably be higher.

The overall rate of survival that was free of an adverse short-term outcome (moderate/severe CLD, NEC requiring surgical treatment, IVH grades 3–4, and ROP grades 3–5) was 86.5% in our study. The overall prevalence of moderate/severe CLD, severe NEC, IVH grades 3 to 4, and severe ROP was 7.3%, 3.1%, 2.1%, and 6.2%, respectively. The outcome results in the EPIPAGE-2 cohort study were similar to those in our study, with a rate of survival that was free of an adverse short-term outcome of 82.9% for those born between 23 and 31 weeks of gestation.[27] Furthermore, the prevalence of moderate/severe CLD, severe NEC, IVH, and severe ROP was 8.0%, 3.7%, 5.3%, and 1.2%, respectively. Other studies that only focussed on extremely preterm infants reported markedly higher frequencies of short-term morbidities.[16,20,30] The prevalence of severe CLD in other studies ranged from 25%[30] to 44%,[20] and the prevalence of severe ROP ranged from 8%[16] to 34%.[30] The lowest prevalence of severe IVH in extremely preterm infants was 6.0% in a Swedish study,[19] 6.9% in a Dutch Study,[16] and 5.3% in another study that included extremely preterm and very preterm infants.[27] The mean incidence of NEC was reported to be 7% to 10% among extremely preterm infants.[31] In the EPIPAGE-2 cohort, the rate of severe NEC was 3.7% in children born between 23 and 31 weeks of gestation.[27]

A total of 335 (75.8%) of 442 children showed normal motor and mental development at a corrected age of 2 years. Reported rates of no developmental impairment or disability using Bayley assessment at 2 years old in surviving infants vary from 70.6% in the Netherlands[16] to 52.1% in Australia,[32] and 42% in Sweden.[18] All of these studies reported outcomes of extremely preterm infants only. The EPIPAGE-2 cohort study reported a much better outcome, where 80.5% of all children born between 23 and 31 weeks of gestation survived without neuromotor or sensory disability at 2 years of corrected age.[33] However, Bayley assessment for the definition of outcome was not used in this cohort. Generally, developmental outcomes are difficult to compare because of different testing methods and different definitions of disability used.

Our study showed no difference in neurodevelopmental outcome at 1 and 2 years

of age between the human milk and formula groups as assessed with Bayley-II and Bayley-III. This result might be explained by the high breastfeeding rate of 81.4% at discharge from hospital. This finding may also be explained by the local feeding strategy using only human milk in neonates who weighed less than 1000 g and mother's milk or donor milk if available in neonates who weighed 1000 to 1500 g. Our results are in accordance with a recently published study by O'Connor et al.[34] These authors did not find an improved outcome in very low birth weight infants at 18 months of corrected age when supplemental donor milk instead of formula was provided as a supplement to mother's milk. The authors concluded that if donor milk is used in settings with high provision of mother's milk, improved neurodevelopmental outcome should not be considered a treatment goal.

The strengths of this study include the population-based cohort design with prospective enrolment of infants who were born not only extremely preterm, but also very preterm. These outcomes have been reported infrequently. Moreover, the effect of feeding during hospital stay was included in the outcome data. Specialists in paediatrics and paediatric neurology performed the follow-up examinations and certified psychologists administered the Bayley-II and Bayley-III tests.

A limitation of our study is the number of children who were lost to follow-up, although follow-up rates at 1 and 2 years of age were high at 87.1% and 83.9%, respectively. However, we found a social bias in participation, with more mothers who smoked during pregnancy refusing to participate in follow-up. Another limitation is the early age at follow-up because cognitive and academic problems may become evident later.[35] Additionally, our study focussed on outcome differences regarding feeding strategy and was not a randomized, controlled trial. However, randomization between human milk and formula would not have been possible for ethical reasons. Moreover, only differences in outcome between those fed with any human milk and those fed with formula at discharge were calculated. This is because the precise amount of human milk could not be extracted from patients' records retrospectively.

This study provides the first complete description of outcome of very preterm infants who were born in Tyrol. To compare these data with those of other populations, the Austrian healthcare system and policy on treatment of very preterm infants must be considered. Healthcare in Austria is accessible for all people and everyone has health insurance coverage. Perinatal care is well structured and offered to every pregnant woman. This health system may lead to better care in pregnancy and might also be an explanation for good outcome data in very preterm infants.

Conclusions

Our population-based study of very preterm infants shows that mortality and short-term morbidity rates are low. There is no difference in short-term morbidity or neurodevelopmental outcome at 1 or 2 years of corrected age between infants who are fed with human milk at discharge and those who are formula-fed. Advances in perinatal and neonatal care, as well as the high rate of human milk feeding during hospital stay, play an important role in a successful strategy for low rates of complications in these children.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. EXPRESS Group, Fellman V, Hellström-Westas L, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009; 301: 2225–2233.
2. Bolisetty S, Dhawan A, Abdel-Latif M, et al. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. *Pediatrics* 2014; 133: 55–62.
3. Larroque B, Ancel PY, Marret S, et al. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet* 2008; 371: 813–820.
4. Schanler RJ, Shulman RJ and Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics* 1999; 103: 1150–1157.
5. Schanler RJ, Lau C, Hurst NM, et al. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics* 2005; 116: 400–406.
6. Maayan-Metzger A, Avivi S, Schushan-Eisen I, et al. Human milk versus formula feeding among preterm infants: short-term outcomes. *Am J Perinatol* 2012; 29: 121–126.
7. Vohr BR, Poindexter BB, Dusick AM, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics* 2006; 118: e115–e123.
8. Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics* 2007; 120: e953–e959.
9. Fenton TR and Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013; 13: 59.
10. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg* 1978; 187: 1–7.
11. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. *J Pediatr* 1978; 92: 529–534.
12. An international classification of retinopathy of prematurity. Committee for the classification of retinopathy of prematurity. *Arch Ophthalmol* 1984; 102: 1130–1134. (https://www.ncbi.nlm.nih.gov/pubmed/6547831)
13. Bayley N. *Bayley scales of infant and toddler development*. 2nd ed. San Antonio, TX: Psychological Corporation, 1993.
14. Bayley N. *Bayley scales of infant and toddler development*. 3rd ed. San Antonio, TX: Harcourt Assessment, 2006.
15. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther* 2000; 80: 974–985.
16. de Waal CG, Weisglas-Kuperus N, van Goudoever JB, et al. Mortality, neonatal morbidity and two year follow-up of extremely preterm infants born in The Netherlands in 2007. *PLoS One* 2012; 7: e41302.
17. Larroque B, Breart G, Kaminski M, et al. Survival of very preterm infants: epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed* 2004; 89: F139–F144.
18. Serenius F, Källén K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA* 2013; 309: 1810–1820.
19. Markestad T, Kaaresen PI, Rønnestad A, et al. Early death, morbidity, and need of

treatment among extremely premature infants. *Pediatrics* 2005; 115: 1289–1298.
20. Vanhaesebrouck P, Allegaert K, Bottu J, et al. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. *Pediatrics* 2004; 114: 663–675.
21. Chan K, Ohlsson A, Synnes A, et al. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. *Am J Obstet Gynecol* 2001; 185: 220–226.
22. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. *Pediatrics* 2010; 126: 443–456.
23. Costeloe KL, Hennessy EM, Haider S, et al. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ* 2012; 345: e7976. doi: 10.1136/bmj.e7976
24. Boland RA, Davis PG, Dawson JA, et al. Predicting death or major neurodevelopmental disability in extremely preterm infants born in Australia. *Arch Dis Child Fetal Neonatal Ed* 2013; 98: F201–F204. doi: 10.1136/archdischild-2012–301628
25. Berger TM, Steurer MA, Woerner A, et al; Swiss neonatal network. Trends and centre-to-centre variability in survival rates of very preterm infants (<32 weeks) over a 10-year-period in Switzerland. *Arch Dis Child Fetal Neonatal Ed* 2012; 97: F323–F328.
26. Younge N, Goldstein RF, Cotten CM, et al. Survival and neurodevelopment of perivi-able infants. *N Engl J Med* 2017; 376: 1890–1891. doi: 10.1056/NEJMc1703379
27. Ancel PY, Goffinet F, EPIPAGE-2 Writing Group, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr* 2015; 169: 230–238. doi: 10.1001/jamapediatrics.2014.3351
28. Mercier CE, Dunn MS, Ferrelli KR, et al. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998–2003. *Neonatology* 2010; 97: 329–338. doi: 10.1159/000260136
29. Field DJ, Dorling JS, Manktelow BN, et al. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994–9 compared with 2000–5. *BMJ* 2008; 336: 1221–1223. doi: 10.1136/bmj.39555.670718.BE
30. EXPRESS Group. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). *Acta Paediatr* 2010; 99: 978–992. doi: 10.1111/j.1651–2227.2010.01846.x
31. Thompson AM and Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. *Drugs* 2008; 68: 1227–1238.
32. Doyle LW, Roberts G, Anderson PJ, et al. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. *J Pediatr* 2010; 156: 49–53.e1. doi: 10.1016/j.jpeds.2009.07.013
33. Pierrat V, Marchand-Martin L, Arnaud C, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. *BMJ* 2017; 358: j3448. doi: 10.1136/bmj.j3448
34. O'Connor DL, Gibbins S, Kiss A, et al. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial. *JAMA* 2016; 316: 1897–905. doi: 10.1001/jama.2016.16144
35. Aarnoudse-Moens CS, Oosterlaan J, Duivenvoorden HJ, et al. Development of preschool and academic skills in children born very preterm. *J Pediatr* 2011; 158: 51–56.