Revisión de (*algunos*) Ensayos Aleatorizados y Controlados en Neonatología

1° Congreso Argentino de Neonatología

2010


Systematic Reviews
and Meta-analyses
Randomized
Controlled Double
Blind Studies
Cohort Studies
Case Control Studies
Case Series
Case Reports
Ideas, Editorials, Opinions
Animal research
In vitro ('test tube') research

APRECIACIÓN CRÍTICA DE LA LITERATURA MÉDICA

MBE

⇒ formulación de preguntas contestables para valorar:

VALIDEZ	**Metodología**
IMPORTANCIA	**Resultados**
APLICABILIDAD	**Implicancias**

Sackett DL, MBE 2001

APRECIACIÓN CRÍTICA DE LA LITERATURA MÉDICA

Fuentes

- "Users' Guides to the Medical Literature" G Guyatt et al / JAMA
- "How to read a Paper" T Greenhalgh / BMJ
- Tips for learners , CMAJ
- CONSORT
- Etc.

Grupo CONSORT

	Item number	Descriptor	Reported on page number
Title and abstract	1	How participants were allocated to interventions (eg, "random allocation", "randomised", or "randomly assigned").	
Introduction			
Background	2	Scientified background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors, &c).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomisation			
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were aware of group assignment. If not, how the success of masking was assessed.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State the results in absolute numbers when feasible (eg, 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (eg, 95% CI).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side-effects in each intervention group.	
Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	
Generalisability	21	Generalisability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

Checklist of items to include when reporting a randomised trial

*Guidelines for evaluating single studies of therapeutic interventions**

Aspect	Evaluative questions
Design	Were patients randomly allocated to treatment groups? Was treatment allocation adequately concealed? Were patients, health workers, and study personnel "blind" to treatment? Was sample size adequate?
Analysis	Were groups similar at the start of the trial? Were groups treated equally during the trial? How complete was follow-up? Were patients analyzed in the groups to which they were allocated (intention-to-treat analysis)? Was "data dredging" avoided?
Reporting	How large was the treatment effect? How precise was the estimate of treatment effect? How complete was study reporting?
Applying study findings	Can the results be applied to patients in my care? Were all clinically important outcomes considered? Do the treatment benefits outweigh the potential harms?

*Adapted from Guyatt et al.[4,5]

Selección de ensayos?

- Arbitraria y subjetiva
- Relevancia /Implicancias /Controversia
- Cómo extrapolar a nuestra práctica?
- Métodos de apreciación crítica…algo más?
- Como hacer que nos sirva en el día a día?
- Motivar discusión
- Aún los mejores estudios pueden ser analizados con buena fe (ejercicio metodológico)

1) TIPP (Schmidt et al NEJM 2001)
2) CAP (Schmidt et al NEJM 2006-2007)
3) UK ECMO (Lancet 1996)

The New England Journal of Medicine

LONG-TERM EFFECTS OF INDOMETHACIN PROPHYLAXIS IN EXTREMELY-LOW-BIRTH-WEIGHT INFANTS

BARBARA SCHMIDT, M.D., PETER DAVIS, M.D., DIANE MODDEMANN, M.D., ARNE OHLSSON, M.D., ROBIN S. ROBERTS, M.SC., SAROJ SAIGAL, M.D., ALFONSO SOLIMANO, M.D., MICHAEL VINCER, M.D., AND LINDA L. WRIGHT, M.D., FOR THE TRIAL OF INDOMETHACIN PROPHYLAXIS IN PRETERMS INVESTIGATORS*

- La administración profiláctica de indometacina reduce la incidencia de DAP y de HIV severa en RNMBP (Bandstra 1988, Ment 1994)
- Mecanismos no del todo claros → podrían incluir la ↓ perfusión cerebral /isquemia
- Importancia de conocer efectos sobre neurodesarrollo a largo plazo (Ment 1996, 2000)
- Determinar si la I.M. profiláctica mejora la sobrevida sin discapacidad en RNEBP

The New England Journal of Medicine

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- RNPT de 500-999g a las 2hs de vida
- Internacional 32 centros (Canada, EEUU, Australia & Nueva Zelanda)
- Enero 1996-Marzo 1998
- Random. OK, Estratificado por peso y por centro
- Intervención → Indo 0.1 /kg vs Placebo (x 3)
- Enmascarado y Ciego
- Outcome 1°: Muerte o Trastorno desarrollo a los 18m EC (Clara y extensamente definido, lo mismo que las formas de evaluarlo)
- Idem para los multiples outcomes 2°
- No lo plantean en forma de hipótesis
- Análisis estadístico bien definido (ajustado x estrato PN y centro)
- NO REPORTAN CALCULO DE TAMAÑO MUESTRAL (POST HOC?)

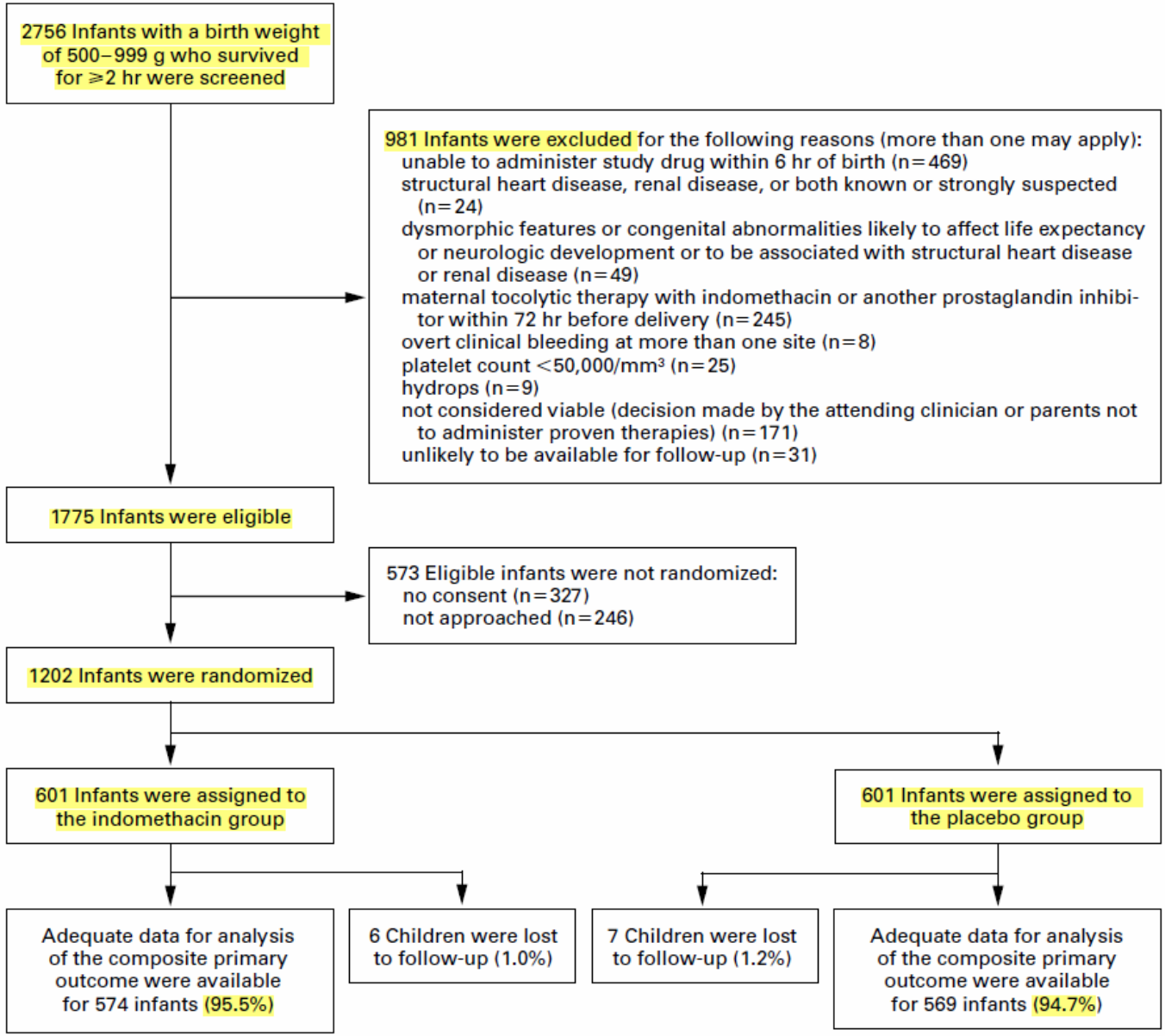

Figure 1. Numbers of Infants Who Were Screened and Randomly Assigned to the Indomethacin and Placebo Groups, and Numbers for Whom Follow-up Data Were Available.

TABLE 3. PRIMARY OUTCOME OF DEATH OR NEUROSENSORY IMPAIRMENT.*

OUTCOME	EVENT RATE		ODDS RATIO		
	INDOMETHACIN GROUP	PLACEBO GROUP	UNADJUSTED	ADJUSTED (95% CI)	P VALUE
	no./total no. (%)				
Composite					
Death or impairment	271/574 (47)	261/569 (46)	1.1	1.1 (0.8–1.4)	0.61
Components					
Death before 18 mo of corrected age†	125/595 (21)	111/594 (19)	1.2	1.2 (0.9–1.6)	0.27
Cerebral palsy‡	58/467 (12)	55/477 (12)	1.1	1.1 (0.7–1.6)	0.64
Cognitive delay (MDI <70)‡	118/444 (27)	117/457 (26)	1.1	1.0 (0.8–1.4)	0.86
Hearing loss requiring amplification‡	10/456 (2)	10/466 (2)	1.0	1.0 (0.4–2.5)	0.93
Bilateral blindness‡	9/465 (2)	7/472 (1)	1.3	1.3 (0.5–3.6)	0.58

*Odds ratios have been adjusted for the birth-weight stratum and center, except for the odds ratios for hearing loss and bilateral blindness, which were adjusted only for the birth-weight stratum. P values are for the adjusted odds ratios. CI denotes confidence interval, and MDI Mental Development Index.

†These data do not include the 13 infants who were lost to follow-up at 18 months.

‡Data for this outcome exclude infants who died before scheduled tests and those who were alive but were not tested or were lost to follow-up.

TABLE 4. LONG-TERM AND SHORT-TERM SECONDARY OUTCOMES IN THE INFANTS IN THE INDOMETHACIN AND PLACEBO GROUPS.

OUTCOME	EVENT RATE		ODDS RATIO*		
	INDOMETHACIN GROUP	PLACEBO GROUP	UN-ADJUSTED	ADJUSTED (95% CI)	P VALUE
	no./total no. (%)				
Long-term					
Hydrocephalus with shunt†	15/470 (3)	9/480 (2)	1.7	1.7 (0.7–3.9)	0.21
Seizure disorder†	8/470 (2)	7/483 (1)	1.2	1.2 (0.4–3.3)	0.76
Microcephaly†	49/461 (11)	54/475 (11)	0.9	0.9 (0.6–1.4)	0.77
Short-term					
Patent ductus arteriosus	142/601 (24)	301/601 (50)	0.3	0.3 (0.2–0.4)	<0.001
Indomethacin for closure of patent ductus arteriosus	100/601 (17)	276/601 (46)	0.2	0.2 (0.2–0.3)	<0.001
Surgical closure of patent ductus arteriosus	40/601 (7)	74/601 (12)	0.5	0.5 (0.3–0.8)	0.001
Pulmonary hemorrhage	89/601 (15)	98/601 (16)	0.9	0.9 (0.6–1.2)	0.45
Need for supplemental oxygen at postmenstrual age of 36 wk‡	225/496 (45)	215/503 (43)	1.1	1.2 (0.9–1.5)	0.26
Need for supplemental oxygen at discharge to home§	97/487 (20)	88/496 (18)	1.2	1.2 (0.9–1.6)	0.32
Necrotizing enterocolitis	64/601 (11)	58/601 (10)	1.1	1.1 (0.8–1.7)	0.53
Gastrointestinal perforation	36/601 (6)	32/601 (5)	1.1	1.2 (0.7–1.9)	0.56
Periventricular or intraventricular hemorrhage†	236/569 (41)	234/567 (41)	1.0	1.0 (0.8–1.3)	0.86
Severe (grade 3 or 4) periventricular or intraventricular hemorrhage†	52/569 (9)	75/567 (13)	0.7	0.6 (0.4–0.9)	0.02
Intraparenchymal echodensities, periventricular leukomalacia, porencephalic cysts, or ventriculomegaly†	125/563 (22)	142/562 (25)	0.8	0.8 (0.6–1.1)	0.23
Bilateral retinopathy†	315/507 (62)	301/521 (58)	1.2	1.2 (0.9–1.6)	0.16

*Odds ratios have been adjusted for the birth-weight stratum and center, except for the odds ratios for hydrocephalus, seizure disorder, microcephaly, and need for oxygen at discharge to home, which have been adjusted only for the birth-weight stratum. P values are for the adjusted odds ratios. CI denotes confidence interval.

The New England Journal of Medicine

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Conclusiones:

I.M. Profiláctica no mejora la sobrevida sin discapacidad a los 18 meses

Mejora el DAP sin alterar DBP ni Neurodesarrollo

Mejora HIC (ojo las severas eran pocas!) sin mejorar el desarrollo

Entonces:

Como se interpreta?

La indico o no?

Para qué la indico?

En qué pacientes?

En qué UCIN?

APRECIACIÓN CRÍTICA DE LA LITERATURA MÉDICA

MBE

⇒ formulación de preguntas contestables para valorar:

VALIDEZ	**Metodología**	**OK**
IMPORTANCIA	**Resultados**	**±**
APLICABILIDAD	**Implicancias**	**++++**

Sackett DL, MBE 2001

The New England Journal of Medicine

LONG-TERM EFFECTS OF INDOMETHACIN PROPHYLAXIS IN EXTREMELY-LOW-BIRTH-WEIGHT INFANTS

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Valorar:

1) Efecto sobre DAP (DBP?) *NNT 20 para prevenir Cx*
2) Efecto sobre HIC *NNT 25 para prevenir HIC severa*
3) Efecto sobre resultados a largo plazo

Utilización:

Variable, debería depender de resultados locales? Validez externa?

Valor que tienen los estudios “accesorios” o análisis post hoc (Transformar la población en una cohorte)

Why Does Indomethacin Prophylaxis Prevent PDA but not BPD?

	Indomethacin	Placebo	
PDA	57/105 (54%)	132/241 (55%)	
No PDA	183/391 (43%)	83/262 (32%)	0.015

Schmidt B et. al. APS-SPR 2003

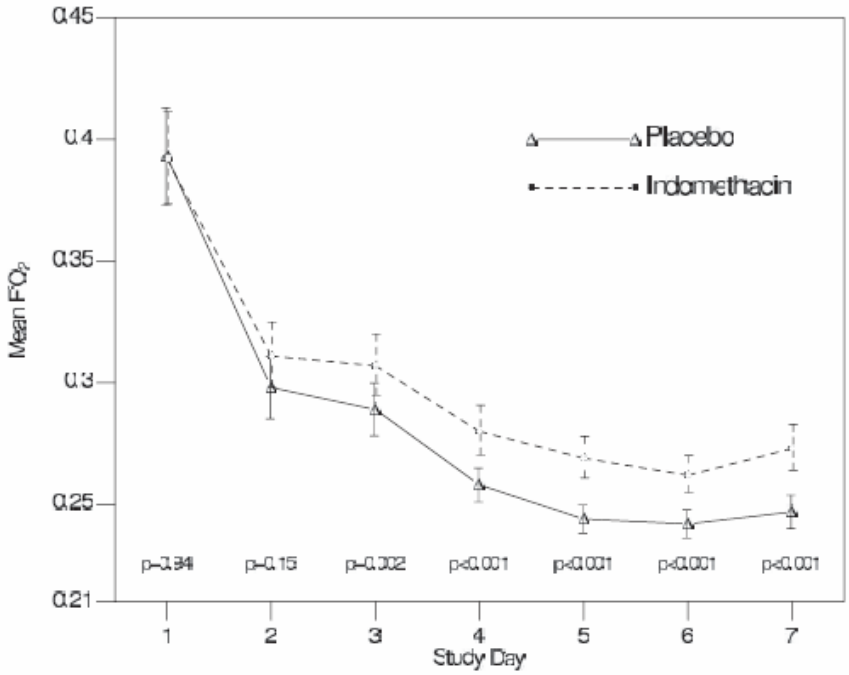
Why Does Indomethacin Prophylaxis Prevent PDA but not BPD?

	Indomethacin	Placebo	P Value
FiO2 d7	0.27	0.24	0.0001
% BWt d7	- 4.6	- 10.4	0.0001

Schmidt B et. al. APS-SPR 2003

INDOMETHACIN PROPHYLAXIS, PATENT DUCTUS ARTERIOSUS, AND THE RISK OF BRONCHOPULMONARY DYSPLASIA: FURTHER ANALYSES FROM THE TRIAL OF INDOMETHACIN PROPHYLAXIS IN PRETERMS (TIPP)

BARBARA SCHMIDT, MD, MSc, ROBIN S. ROBERTS, MSc, AVROY FANAROFF, MD, PETER DAVIS, MD, HARESH M. KIRPALANI, MD, MSc, CHUKS NWAESEI, MD, MICHAEL VINCER, MD, AND THE TIPP INVESTIGATORS*



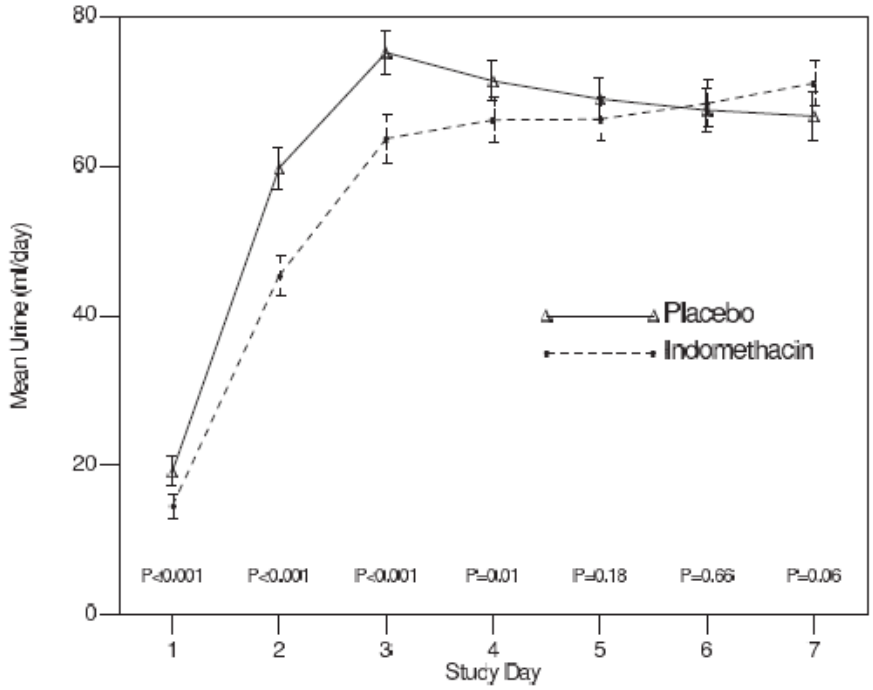


Table I. Interaction between indomethacin prophylaxis, PDA, and the risk of BPD

	Indomethacin prophylaxis	Placebo	*P* value
Incidence of PDA	105/496 (21%)	246/503 (49%)	<.000005
Incidence of BPD	225/496 (45%)	215/503 (43%)	.41
Risk of BPD by PDA status			
PDA	55/105 (52%)	137/246 (56%)	*P* (Interaction)
No PDA	170/391 (43%)	78/257 (30%)	.015

Table II. Logistic regression of BPD in infants without PDA

	Model 1: Unadjusted			Model 2: Adjusted for baseline variables			Model 3: Adjusted for baseline and explanatory variables		
Variable	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Indomethacin Prophylaxis	1.77	1.27–2.46	<.0001	1.50	1.05–2.15	.027	1.12	0.76–1.66	.57
Gestational Age				0.78	0.70–0.87	<.0001	0.81	0.72–0.91	.0005
Male gender				1.52	1.08–2.14	.017	1.49	1.05–2.12	.027
Multiple Birth				1.03	0.69–1.55	.87	1.10	0.72–1.68	.65
FiO_2 on day 1				1.02	1.01–1.03	<.0001	1.02	1.01–1.03	.0002
Intubated on day 1				2.16	1.10–4.24	.026	1.97	1.00–3.85	.05
Antenatal Steroids				1.10	0.88–1.78	.69	1.07	0.65–1.76	.79
FiO_2 (Day 6–7)*							1.07	1.04–1.09	<.0001
Weight loss (Day 6–7)*							1.03	1.01–1.05	.012

CI, confidence interval.
*If data for day 7 were missing, then data from day 6 were used instead.

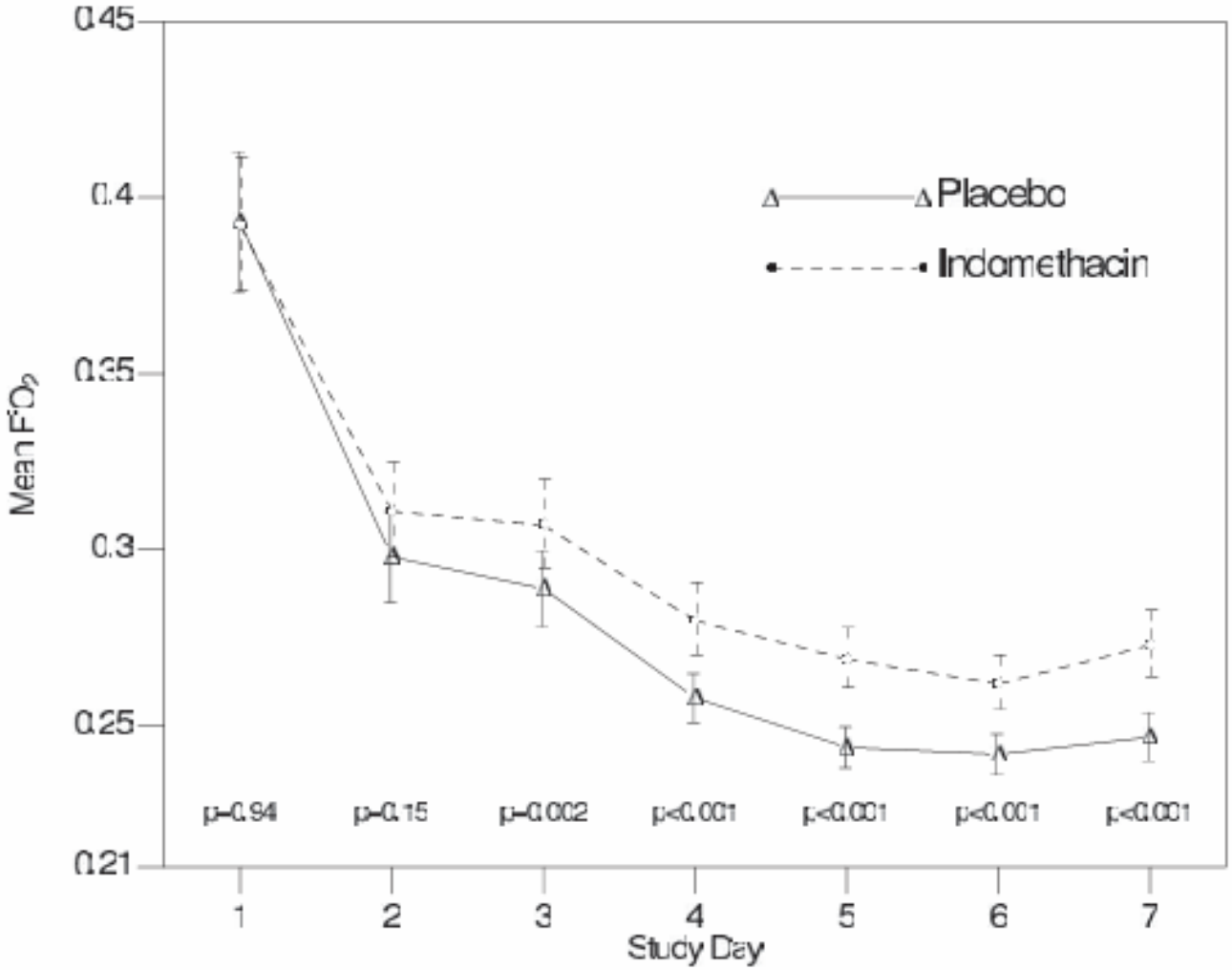


Figure 1. Supplemental oxygen requirements in the indomethacin and placebo groups. The daily mean fraction of supplemental oxygen is plotted with 95% confidence intervals during the first week of life for 999 ELBW infants who were randomized to prophylactic indomethacin (n = 496) or placebo (n = 503) soon after birth and who survived to postmenstrual age 36 weeks.

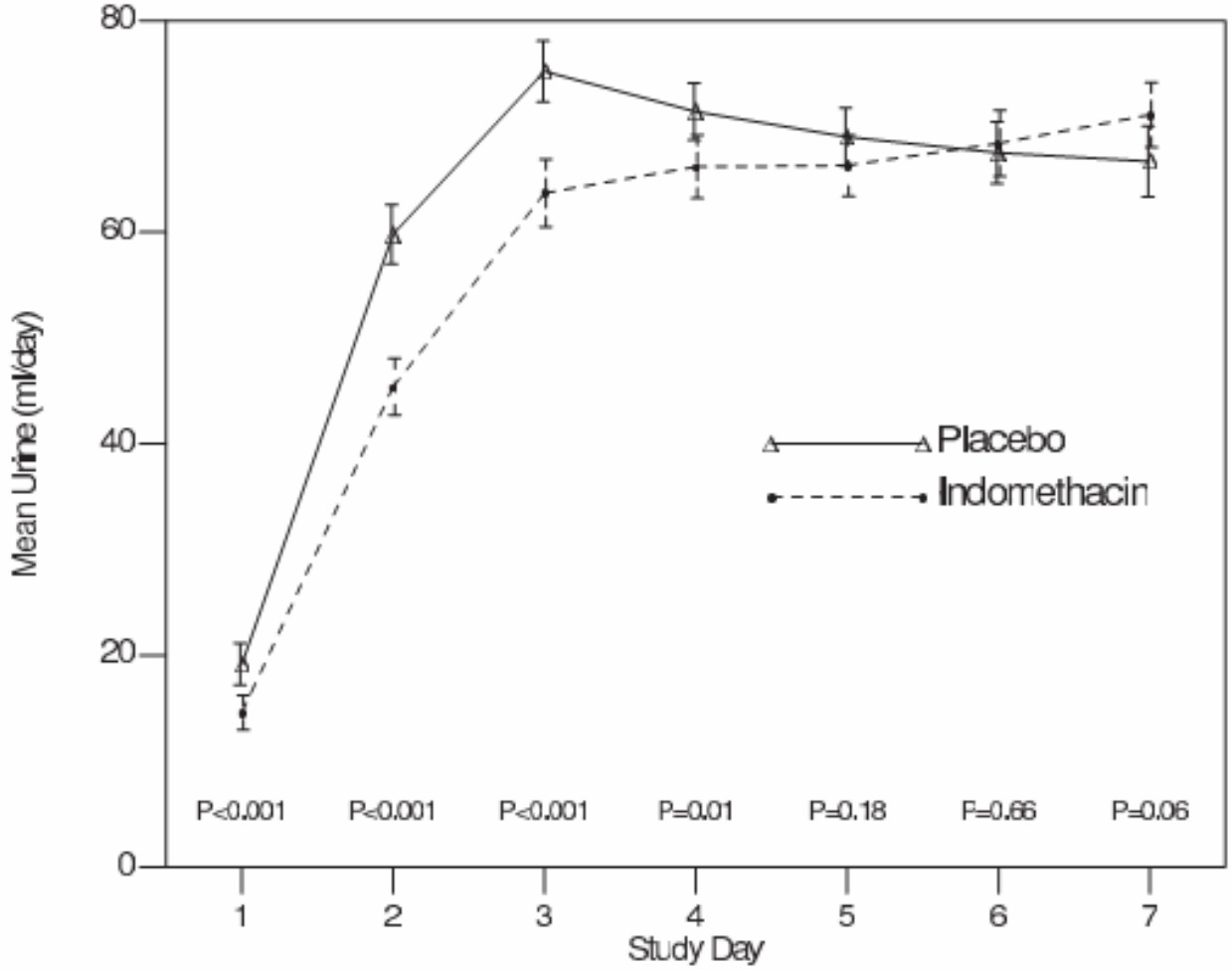


Figure 2. Urine volumes in the indomethacin and placebo groups. The daily mean urine volume is plotted with 95% confidence intervals during the first week of life for 999 ELBW infants who were randomized to prophylactic indomethacin (n = 496) or placebo (n = 503) soon after birth and who survived to postmenstrual age 36 weeks.

Neurosensory Impairment after Surgical Closure of Patent Ductus Arteriosus in Extremely Low Birth Weight Infants: Results from the Trial of Indomethacin Prophylaxis in Preterms

Nandkishor S. Kabra, MD, Barbara Schmidt, MD, MSc, Robin S. Roberts, MSc, Lex W. Doyle, MD, Luann Papile, MD, Avroy Fanaroff, MD, and the Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators*

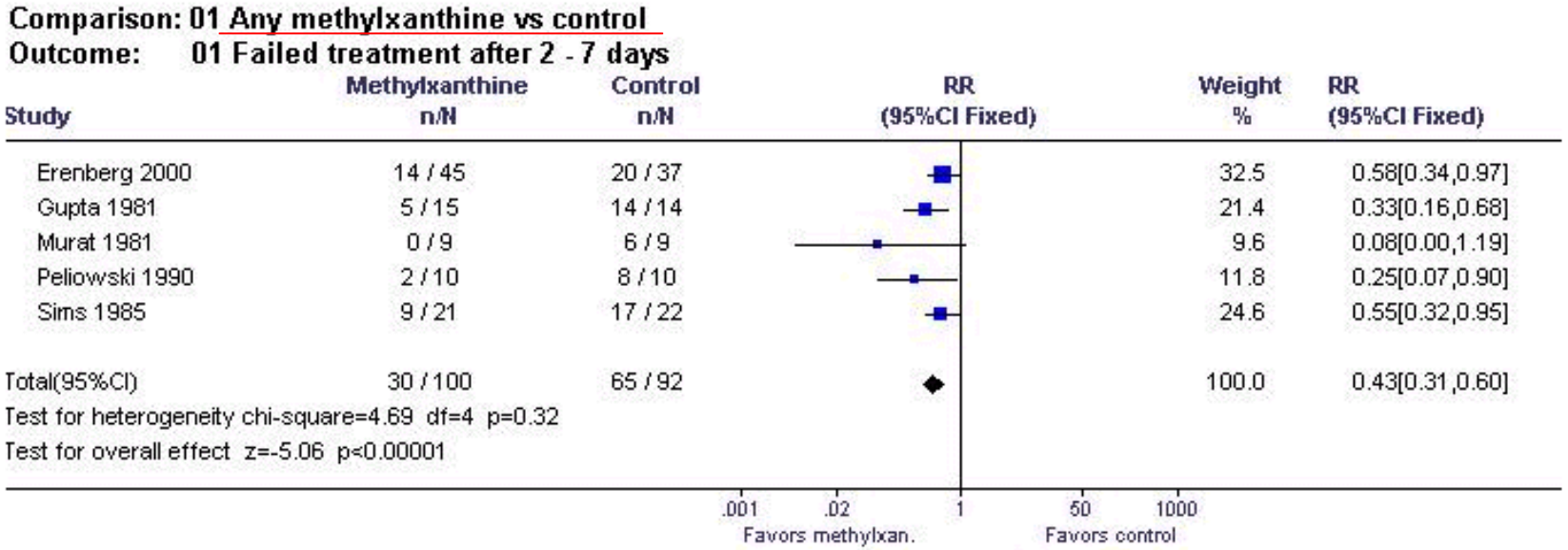
Objectives To determine whether surgical closure of a patent ductus arteriosus (PDA) is a risk factor for bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity (ROP), and neurosensory impairment in extremely low birth weight (ELBW) infants.

Study design We studied 426 infants with a symptomatic PDA, 110 of whom underwent PDA ligation and 316 of whom received medical therapy only. All infants participated in the multicenter Trial of Indomethacin Prophylaxis in Preterms (TIPP) and were observed to a corrected age of 18 months.

Results Of the 95 infants who survived after PDA ligation, 50 (53%) had neurosensory impairment, compared with 84 of the 245 infants (34%) who survived after receiving only medical therapy (adjusted odds ratio, 1.98; 95% CI, 1.18-3.30; $P = .0093$). BPD (adjusted odds ratio, 1.81; 95% CI, 1.09-3.03; $P = .023$) and severe ROP (adjusted odds ratio, 2.20; 95% CI, 1.19-4.07; $P = .012$) were also more common after surgical PDA closure.

Conclusions PDA ligation may be associated with increased risks of BPD, severe ROP, and neurosensory impairment in ELBW infants. *(J Pediatr 2007;150:229-34)*

Metil-xantinas para apnea del prematuro



Methylxanthine therapy in premature infants: Sound practice, disaster, or fruitless byway?

B. Schmidt, J Pediatr, Oct 1999

Neonatal apnea, bradycardia, or desaturation: Does it matter?

R. Martin & A. Fanaroff, J Pediatr, May 1998

Metil-xantinas para apnea del prematuro

- MX reducen la frecuencia de apnea: es esto de importancia?
- Pocos estudios, pocos pacientes, sin evaluar efectos adversos ni a largo plazo (adenosina protector en hipoxia?, aumento metabolismo basal?)
- Uso extensivo en neonatología $\rightarrow$ estudio CAP proyectó evaluar n=2000/outcome $\rightarrow$ sobrevida sin discapacidad a los 18meses
- Recomendación $\rightarrow$ uso en pacientes seleccionados en base a los efectos conocidos (con > cautela debido a los efectos adversos inciertos)

ORIGINAL ARTICLE

Caffeine Therapy for Apnea of Prematurity

Barbara Schmidt, M.D., Robin S. Roberts, M.Sc., Peter Davis, M.D., Lex W. Doyle, M.D., Keith J. Barrington, M.D., Arne Ohlsson, M.D., Alfonso Solimano, M.D., and Win Tin, M.D., for the Caffeine for Apnea of Prematurity Trial Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 8, 2007 VOL. 357 NO. 19

Long-Term Effects of Caffeine Therapy for Apnea of Prematurity

Barbara Schmidt, M.D., Robin S. Roberts, M.Sc., Peter Davis, M.D., Lex W. Doyle, M.D., Keith J. Barrington, M.D., Arne Ohlsson, M.D., Alfonso Solimano, M.D., and Win Tin, M.D., for the Caffeine for Apnea of Prematurity Trial Group*

ABSTRACT

- Evaluar eficacia y seguridad a corto y largo plazo de la cafeína en RNMBP *(Sin hipotesis nuevamente, forma de reportar estudios "negativos"?)*
- RNPT de 500-1250g candidatos a MX durante los primeros 10 d
- Internacional (Canada, Australia, Europa
- Octubre 1999 - Octubre 2004
- Estratificado por centro
- Intervención → Bolo Cafeina vs SF + diario a 5mg/kg (↑10) "open-label" desaconsejado
- Outcome 1°: Muerte o Trastorno desarrollo a los 18-21m EC (Clara y extensamente definido, lo mismo que las formas de evaluarlo)
- Idem para los multiples outcomes 2°
- Tamaño muestral de 1000 para detectar un ↓ 25% en el outcome 1° (?)
- Análisis estadístico bien definido
- Análisis de corto plazo recomendado por el comité de seguridad

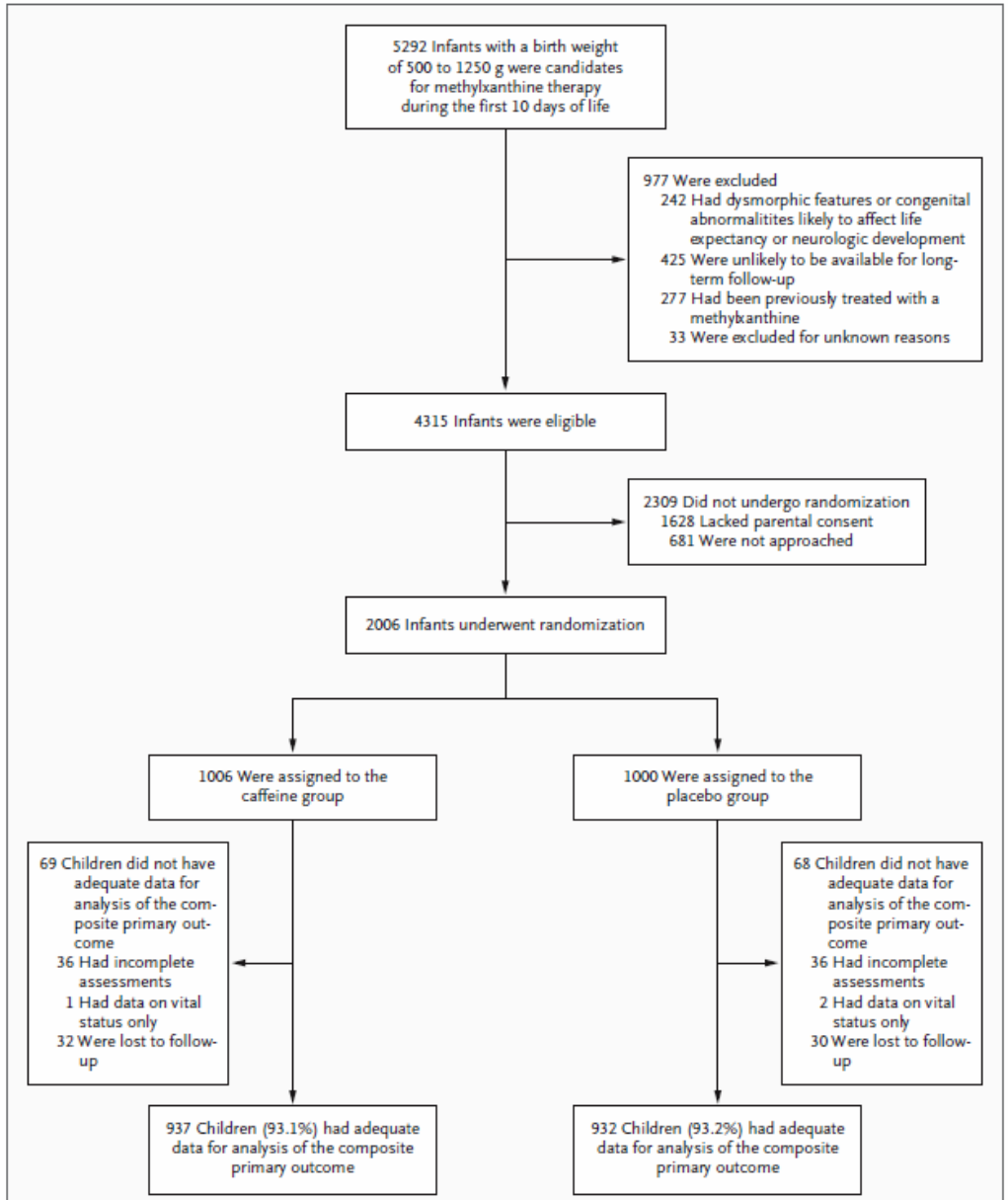


Figure 1. Numbers of Infants Who Were Eligible for the Study, Randomly Assigned to Receive Caffeine Citrate or Placebo, and Followed to a Corrected Age of 18 to 21 Months.

Table 3. Outcomes before the First Discharge Home.*

Outcome	Caffeine Group (N=1006)	Placebo Group (N=1000)	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value	Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)†
Death — no. (%)	52 (5.2)	55 (5.5)	0.94	0.93 (0.63–1.38)	0.73	0.96 (0.64–1.44)
Bronchopulmonary dysplasia — no. (%)‡	350 (36.3)	447 (46.9)	0.65	0.63 (0.52–0.76)	<0.001	0.64 (0.52–0.78)
Retinopathy of prematurity — no. (%)§	322 (39.2)	362 (43.2)	0.84	0.84 (0.68–1.03)	0.09	0.88 (0.70–1.10)
Brain injury — no. (%)¶	126 (13.0)	138 (14.3)	0.90	0.90 (0.69–1.18)	0.44	0.97 (0.74–1.28)
Necrotizing enterocolitis — no. (%)	63 (6.3)	67 (6.7)	0.93	0.93 (0.65–1.33)	0.63	0.94 (0.65–1.34)
Drug therapy only for closure of patent ductus arteriosus — no. (%)‖**	293 (29.3)	381 (38.1)	0.67	0.67 (0.55–0.81)	<0.001	0.67 (0.54–0.82)
Surgical closure of patent ductus arteriosus — no. (%)**	45 (4.5)	126 (12.6)	0.33	0.32 (0.22–0.45)	<0.001	0.29 (0.20–0.43)

Table 2. Primary Outcome of Death or Neurodevelopmental Disability.

Outcome	Caffeine Group	Placebo Group	Unadjusted Odds Ratio	Odds Ratio Adjusted for Center (95% CI)	P Value	Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)*
	no./total no. (%)					
Composite						
Death or disability	377/937 (40.2)	431/932 (46.2)	0.78	0.77 (0.64–0.93)	0.008	0.79 (0.65–0.96)
Components						
Death before 18 mo†	62/974 (6.4)	63/970 (6.5)	0.98	0.97 (0.67–1.40)	0.87	0.99 (0.65–1.50)
Cerebral palsy‡	40/909 (4.4)	66/901 (7.3)	0.58	0.58 (0.39–0.87)	0.009	0.59 (0.39–0.89)
Cognitive delay‡§	293/867 (33.8)	329/858 (38.3)	0.82	0.81 (0.66–0.99)	0.04	0.83 (0.67–1.02)
Severe hearing loss‡¶	17/909 (1.9)	22/905 (2.4)	0.77	0.77 (0.40–1.45)‖	0.41	0.81 (0.43–1.55)‖
Bilateral blindness‡	6/911 (0.7)	8/905 (0.9)	0.74	0.74 (0.26–2.15)‖	0.58	0.79 (0.27–2.31)‖

APRECIACIÓN CRÍTICA DE LA LITERATURA MÉDICA

MBE

⇒ formulación de preguntas contestables para valorar:

VALIDEZ	**Metodología**	**OK**
IMPORTANCIA	**Resultados**	**+++**
APLICABILIDAD	**Implicancias**	**+++ (?)**

Sackett DL, MBE 2001

Metil-xantinas para apnea del prematuro

- Volvimos a usar cafeína *(no sólo no era tan mala son que era buena)*
- Para qué la usamos, apnea, DBP, DAP, Neurodesarrollo? Cómo actúa?
- Una cadena de eventos?
- A quien se la indicamos y cuando?
- Lo hacemos?

Articles

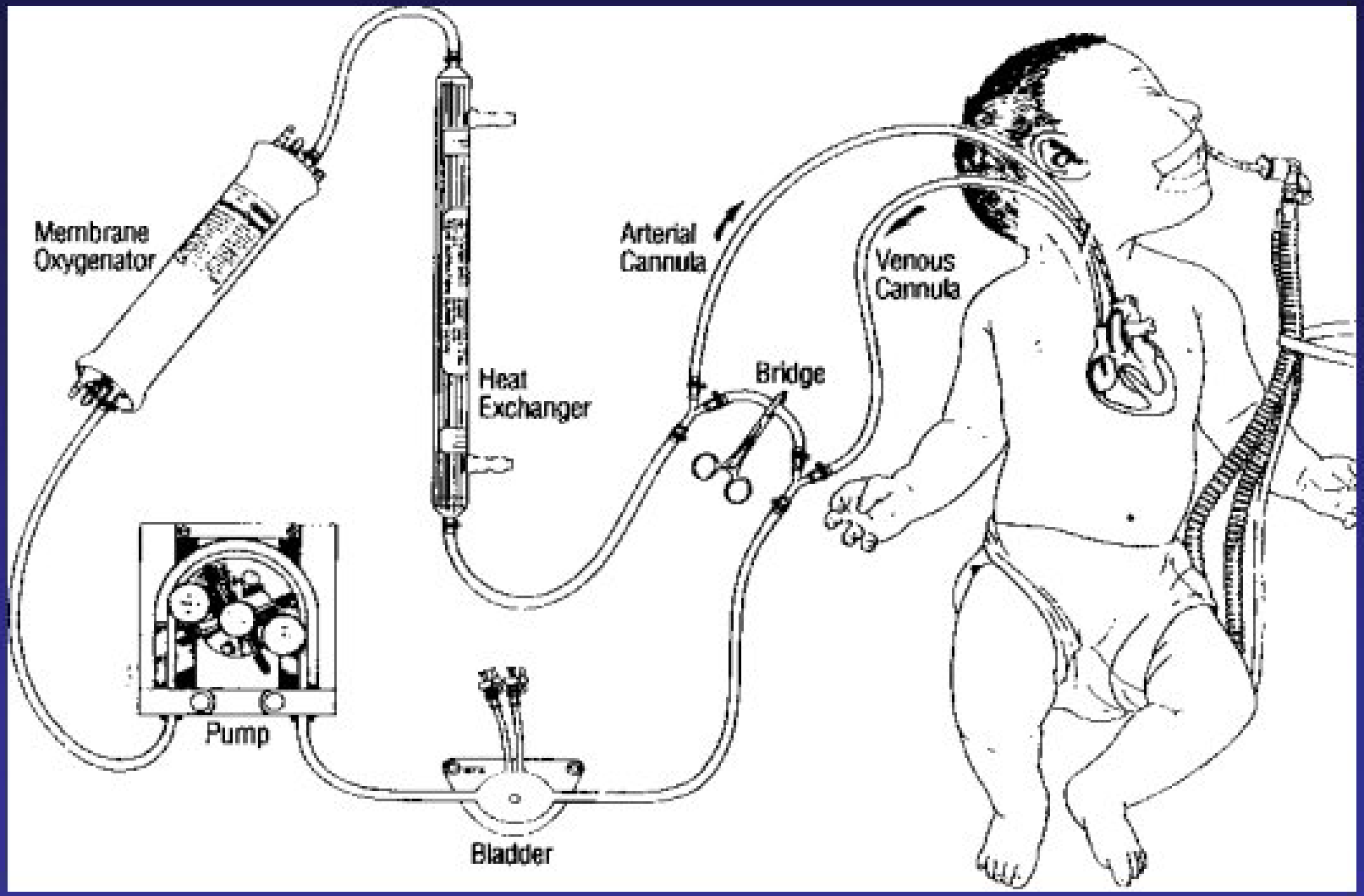
UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation

*UK Collaborative ECMO Trial Group**

Contexto

- ECMO era una técnica costosa y compleja, no exenta de riesgos
- A la vez podía salvar vidas
- Hasta el momento del estudio era controvertida su utilización aunque bastante difundida en los EEUU
- La evidencia disponible provenía del registro ELSO y de series chicas con controles históricos
- Preocupación sobre costo/efectividad y discapacidad en sobrevivientes
- Para poder usarlo dentro del NHS se realizó este EAC

Esquema circuito ECMO



JKS

- Hipótesis: la política de derivación para ECMO reduciría la muerte o sobrevida con discapacidad severa en comparación con el manejo convencional
- Población: RNT con insuficiencia respiratoria severa (IO>40)
- Multicéntrico Reino Unido (55 centros, 5 centros ECMO)
- Entre 1993-1995
- Tamaño muestral=300
- Suspendido tras análisis interino
- Variable principal muerte o discapacidad severa al año
- Intervención

Grupo 1 Derivación a centros ECMO

Grupo 2 Terapia convencional en UCIN Nivel III

Resultados

	ECMO (n=93)	VC (n=92)	RR (95% IC)	%Red Abs (95% IC)
Muerte pre alta	30%	59%	0.51 (0.36-0.73)	29 (15-42)
Muerte al año	32%	59%	0.55 (0.39-0.77)	26 (13-40)*

*NNT: 3.7 (2,5-7.7)

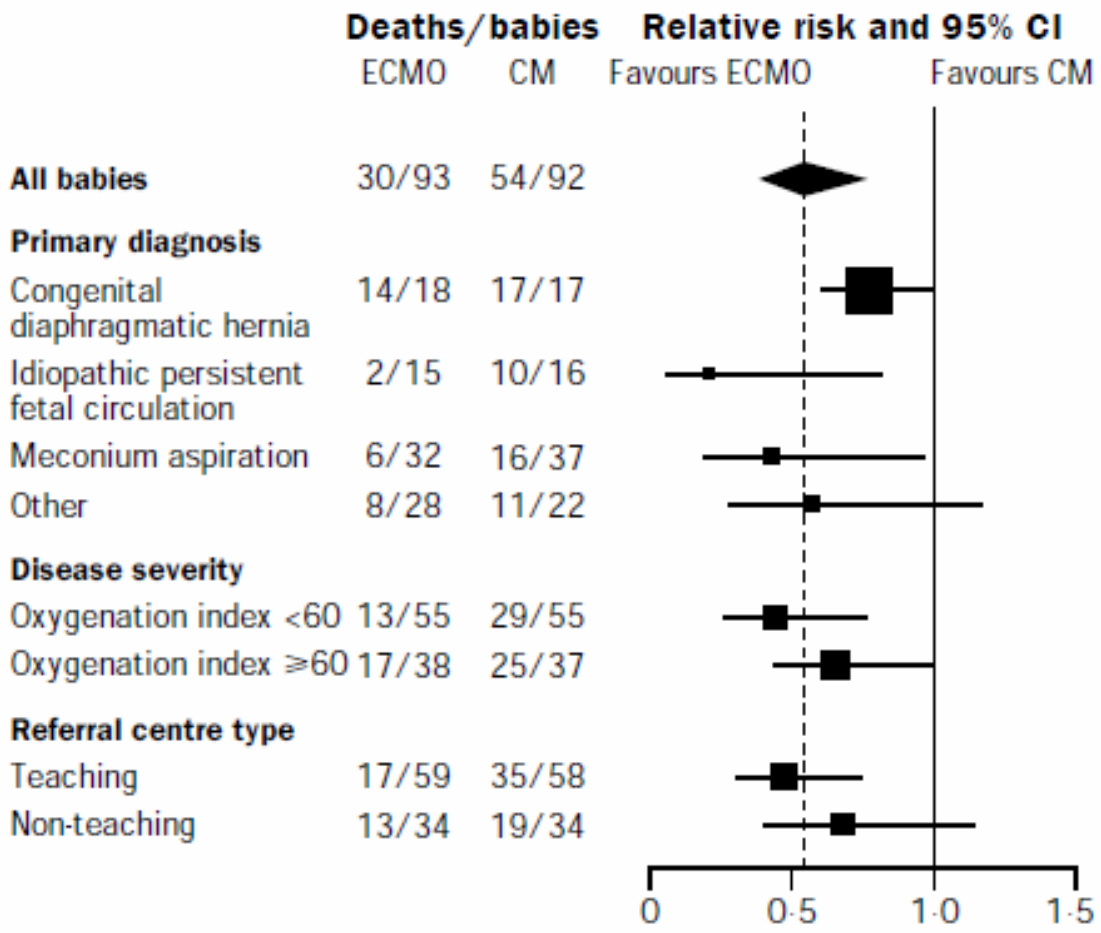
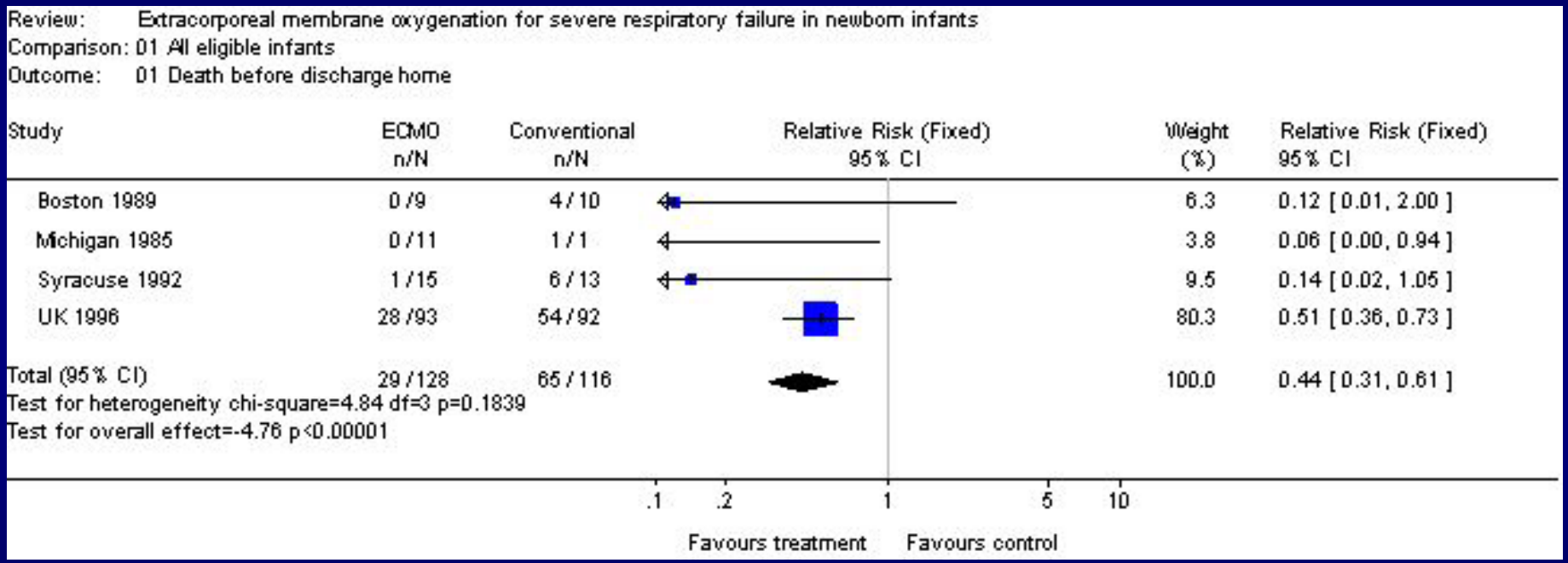


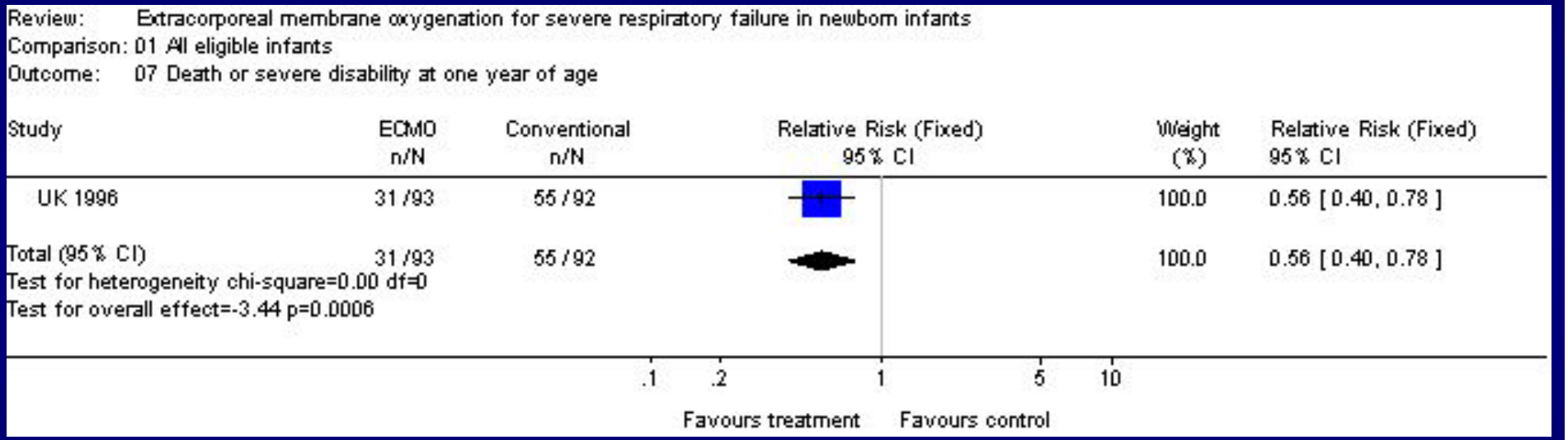
Figure: **Effects of ECMO policy on known deaths**

Relative risks (squares; proportional to amount of information contributed) and 95% CIs (horizontal lines) are plotted for various subgroups. Overall results shown by the diamond. CM=conventional management.

ECMO


Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants
Comparison: 01 All eligible infants
Outcome: 01 Death before discharge home
Study
ECMO n/N
Conventional n/N
Relative Risk (Fixed) 95% CI
Weight (%)
Relative Risk (Fixed) 95% CI
Boston 1989 0/9 4/10 6.3 0.12 [0.01, 2.00]
Michigan 1985 0/11 1/1 3.8 0.06 [0.00, 0.94]
Syracuse 1992 1/15 6/13 9.5 0.14 [0.02, 1.05]
UK 1996 28/93 54/92 80.3 0.51 [0.36, 0.73]
Total (95% CI) 29/128 65/116 100.0 0.44 [0.31, 0.61]
Test for heterogeneity chi-square=4.84 df=3 p=0.1839
Test for overall effect=-4.76 p<0.00001
.1
.2
1
5
10
Favours treatment
Favours control

ECMO


Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants
Comparison: 01 All eligible infants
Outcome: 07 Death or severe disability at one year of age
Study
ECMO n/N
Conventional n/N
Relative Risk (Fixed) 95% CI
Weight (%)
Relative Risk (Fixed) 95% CI
UK 1996
31 /93
55 /92
100.0
0.56 [0.40, 0.78]
Total (95% CI)
31 /93
55 /92
100.0
0.56 [0.40, 0.78]
Test for heterogeneity chi-square=0.00 df=0
Test for overall effect=-3.44 p=0.0006
.1
.2
1
5
10
Favours treatment
Favours control

Evolución alejada

UK collaborative ECMO Trial (4 años)

	ECMO (93)	Control (92)
Mortalidad	33%	59%
Pérdida seguim	2%	3%
Discap grave	3%	0
Discap mod	10%	11%
Discap leve	19%	13%
Sobrev s/discap	30/60(50%)	13/35(37%)

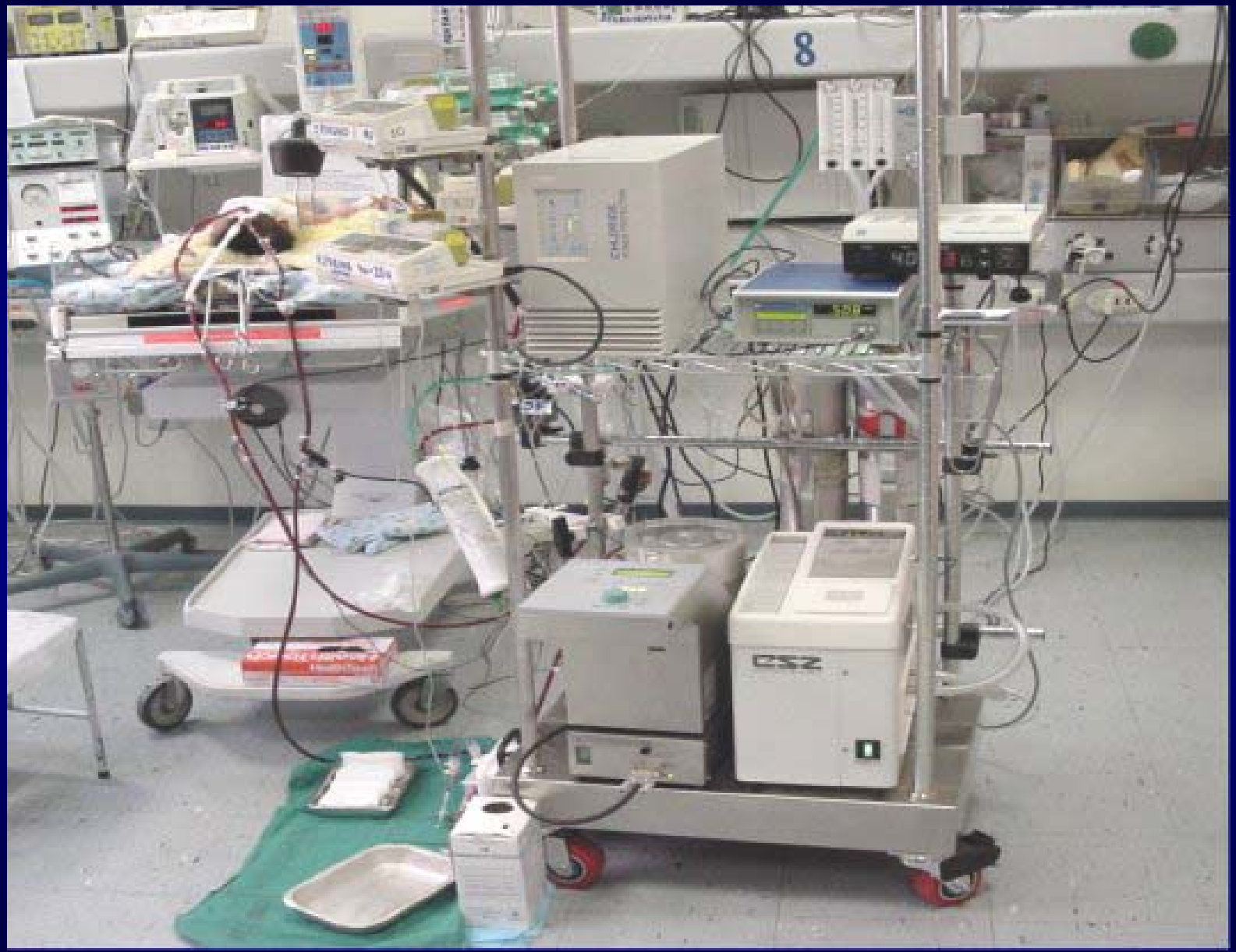
Evolución alejada

UK collaborative ECMO Trial (4 años)

	ECMO	Control
Muerte o Discap grave	37%	59%

RR: 0,64 (0,47-0.86)

Bennett C et al Lancet 2001; 357: 1094-1096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