



UNIVERSIDAD  
SAN SEBASTIAN



# NUEVAS OPCIONES DE TRATAMIENTO FARMACOLOGICO EN DUCTUS ARTERIOSO PERSISTENTE

Dra. Migdy Risco Andrade  
Becada Pediatría HBPM-USS  
Julio 2014

# GENERALIDADES

- DAP es frecuente en RNPT.
- DAP es inversamente proporcional a EG.
- El 55% RNPT < 28 sem. y < 1000 gr. ,DAP con repercusión hemodinámica significativa :
  - alteración de la perfusión cerebral, renal y gastrointestinal.
  - edema pulmonar.
  - insuficiencia cardíaca.

# OPCIONES PARA CIERRE DE DAP

## CIERRE QUIRURGICO

- Eficaz
- Asociado a morbilidad:
- Parálisis cuerda vocal
- Deterioro DBP y neurosensorial

## CIERRE FARMACOLOGICO

- Menos invasivo
- De elección

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis . Neonatology 2012.*

# GENERALIDADES

- Indometacina e IBP endovenoso están disponibles solo en algunos países, y a un alto precio .
- Presentaciones para uso oral disponibles en todo el mundo y a un bajo costo .
- Países en desarrollo han buscado nuevas alternativas para cierre de DAP .
- El 29% de las UCIN Europeas reportaron el uso de ibuprofeno oral para cierre DAP.

*Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants Omer Erdeve y Cols. Arch Dis Child Fetal Neonatal Ed 2012.*

# VALORES ACTUALES

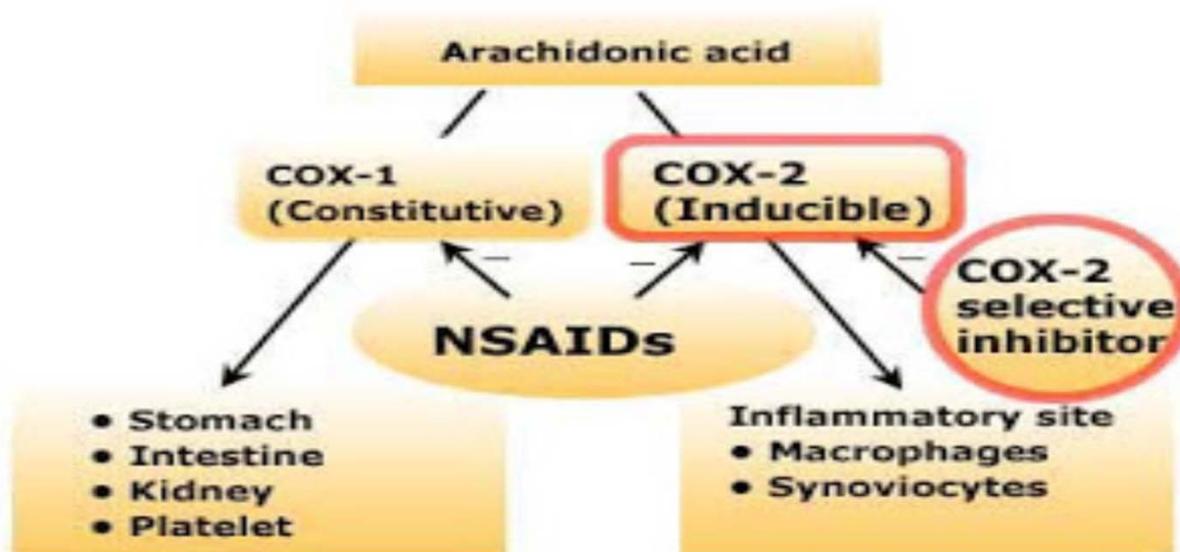
INDOMETACINA EV \$ 312.700 (a)

IBUPROFENO EV \$ 113.600 (a)

IBUPROFENO JARABE \$ 1000-4000 (b)

*Fuente: Unidad de Farmacia HBPM .Año 2014. (a)  
Información de marcas comerciales.Año 2014. (b).*

# MECANISMO ACCION DE LOS AINES



Prostaglandinas: relajan músculo liso e interfieren en el cierre del DAP.

considerar la diferencia de IBP e indometacina en inhibición de COX 1 -COX 2

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis . Neonatology 2012.*

# FARMACOCINETICA

- Concentraciones plasmáticas óptimos de ibuprofeno para el cierre del DAP no están definidos con precisión.
- IBP oral se asocia a un mayor tiempo para alcanzar concentración plasmática.
- IBP oral alcanza concentración plasmática máxima más baja , lo que puede ser adecuada para cierre DAP y con menos eventos adversos.

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis . Neonatology 2012.*

# FARMACOCINETICA

- ¿Como se podría explicar que IBP oral es más eficaz que IBP endovenoso?
  - Se absorbe en el intestino, llega a través de la vena porta a VCI y, en presencia de un foramen oval permeable es desviada al corazón izquierdo.
  - Concentraciones ductales de ibuprofeno pueden ser más altos que si se administra vía oral V/S endovenoso.

# Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis

Roland Neumann<sup>a, b</sup> Sven M. Schulzke<sup>a, b</sup> Christoph Bühner<sup>c</sup>

Neonatology 2012;102:9–15

- **Objetivo** : Revisar sistemáticamente estudios que comparan IBP oral con IBP IV o indometacina IV para el cierre del DAP en RNPT .
- **Métodos:** Se identificaron 107 resúmenes ,seleccionando 5 estudios .
- Dos estudios (n = 166) de buena calidad metodológica que comparan IBP oral con IBP IV y tres ensayos pequeños (n = 92) de moderada calidad metodológica que comparan IBP oral con indometacina IV.

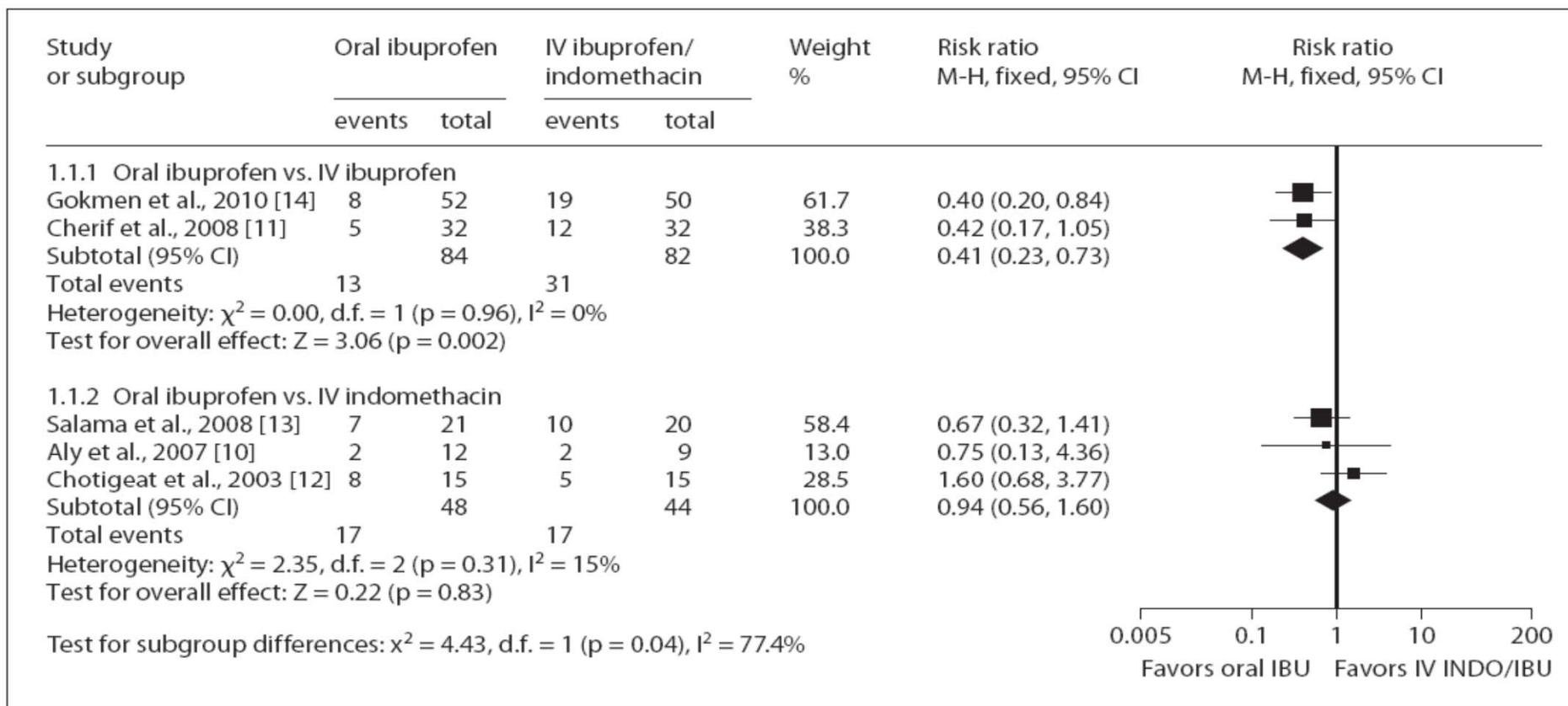
**Table 1.** Characteristics of the studies included

Study	n	Eligibility (GA) weeks	Oral ibuprofen group					Control group				
			n	GA weeks	age days	dose mg/kg/day	duration days	n	GA weeks	age days	dose mg/kg	duration days
<i>Oral ibuprofen vs. IV ibuprofen</i>												
Cherif et al., 2008 [11]	64	<32	32	29.3 (1.2)	2.1 (0.03)	10, 5, 5	3	32	28.3 (1.1)	2.2 (0.03)	10, 5, 5	3
Gokmen et al., 2011 [14]	102	<32	52	28.5 (1.9)	2-4	10, 5, 5	3	50	28.7 (2.1)	2-4	10, 5, 5	3
<i>Oral ibuprofen vs. IV indomethacin</i>												
Chotigeat et al., 2003 [12]	30	<35	15	30.8 (2.3)	6.0 (2.44)	10, 10, 10	3	15	29.9 (2.9)	3.5 (1.6)	0.2, 0.2, 0.2	1
Aly et al., 2007 [10]	21	<35	12	31.2 (2.5)	N/A	10, 10, 5	3	9	32.9 (1.6)	N/A	0.2, 0.2, 0.2	1
Salama et al., 2008 [13]	41	<34	21	27.7 (2.5)	8.1 (1.5)	10, 5, 5	3	20	27.8 (2.8)	7.1 (1.9)	0.2, 0.2, 0.2	1

GA and postnatal age are presented as mean (SD).

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis . Neonatology 2012.*

# OUTCOME PRIMARIO:FRACASO EN CIERRE DAP



- Resultados de esta revisión indican que IBP oral es potencialmente más eficaz que IBP IV y tan eficaz como la indometacina IV para el cierre del DAP en RNPT.

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis . Neonatology 2012.*

# OUTCOME SECUNDARIO

**Table 3.** Meta-analyses comparing oral ibuprofen with standard medical treatment of PDA using IV ibuprofen or IV indomethacin

Outcome	Mean effect <sup>a</sup> (95% CI), n <sup>b</sup>					
	oral ibuprofen vs. IV ibuprofen	ref.	oral ibuprofen vs. IV indomethacin	ref.	Oral ibuprofen vs. IV ibuprofen or IV indomethacin <sup>c</sup>	ref.
Failure of PDA closure	0.41 (0.23, 0.73), 166	11, 14	0.94 (0.56, 1.60), 92	10–13	0.60 (0.41, 0.88), 258	10–14
Mortality	1.22 (0.56, 2.64), 166	11, 14	0.83 (0.31, 2.24), 92	10–13	1.05 (0.54, 1.84), 258	10–14
Serum creatinine, $\mu\text{mol/l}$	-23.9 (-28.3, -19.4), 166	11, 14	-11.5 (-22.1, -0.9), 51	10, 12	-22.1 (-26.5, -17.7), 217	10–12, 14
Necrotizing enterocolitis	0.98 (0.33, 2.90), 166	11, 14	0.53 (0.27, 1.03), 92	10, 12, 13	0.81 (0.48, 1.35), 258	10–14
Gastrointestinal bleeding	2.94 (0.31, 27.70), 166	11, 14	4.77 (0.24, 93.67) 62	10, 13	3.56 (0.60, 21.14), 228	10, 11, 13, 14
Gastrointestinal perforation	not estimable		0.24 (0.03, 1.95), 62	10, 13	0.24 (0.03, 1.95), 228	10, 11, 13, 14
Bronchopulmonary dysplasia	0.79 (0.41, 1.51), 166	11, 14	0.86 (0.38, 1.95), 30	12	0.66 (0.37, 1.16), 196	11, 12, 14
Pulmonary hemorrhage	not estimable		0.15 (0.01, 2.86), 21	10	0.15 (0.01, 2.86), 123	10, 14
Retinopathy of prematurity	0.41 (0.11, 1.51), 102	14	0.98 (0.35, 2.73), 71	12, 13	1.22 (0.74, 2.00), 173	12–14
Intraventricular hemorrhage	1.15 (0.68, 1.95), 166	11, 14	1.62 (0.42, 6.29), 71	12, 13	0.70 (0.15, 3.40), 237	11–14
Periventricular leukomalacia	1.00 (0.15, 6.67), 64	14	0.32 (0.01, 7.38), 41	13	1.03 (0.64, 1.64), 105	11, 13
Sepsis	1.04 (0.58, 1.86), 166	11, 14	1.00 (0.47, 2.15), 30	12	0.67 (0.31, 1.48), 196	11, 12, 14

<sup>a</sup> Results are expressed as relative risk (categorical variables) and weighted mean difference (serum creatinine). <sup>b</sup> Number of study participants included in meta-analysis. <sup>c</sup> Summary effect estimate combining IV ibuprofen and IV indomethacin in control group.

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis . Neonatology 2012.*

# OUTCOME SECUNDARIOS

## EFFECTOS RENALES :

- Con IBP oral niveles de creatinina más bajos.
- Se describen casos IRA transitoria después del uso de ibuprofeno oral .
- Gokmen et al. informó de un aumento significativo de cistatina C.
- Teniendo en cuenta resultados contradictorios, no se pueden extraer conclusiones definitivas y se requiere mayor investigación.

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis . Neonatology 2012.*

# OUTCOME SECUNDARIOS

## EFFECTOS GASTROINTESTINALES :

- Tendencia a menor incidencia de NEC comparando IBP oral v/s indometacina IV.
- Precaución en la interpretación : tres de los cinco estudios incluidos mostraron una inusual alta incidencia de NEC (11-53%) en los RNPT < 28 semanas .

*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis .Roland Neumann a, b Sven M. Schulzke a, b Christoph Bührer c. Neonatology 2012.*

# OUTCOME SECUNDARIOS

## EFECTOS GASTROINTESTINALES :

- Perforación intestinal : 1 caso IBP oral y 4 casos con indometacina ev .
- Hubo más casos de sangrado gastrointestinales después el uso de ibuprofeno oral en comparación con tratamiento ev.
- Resultados contradictorios sobre seguridad gastrointestinal de ibuprofeno oral, por lo cual se debe estudiar el riesgo de efectos adversos gastrointestinales en RNPT MBPN .

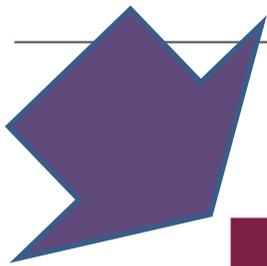
*Oral Ibuprofen versus Intravenous Ibuprofen or Intravenous Indomethacin for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis .Roland Neumann a, b Sven M. Schulzke a, b Christoph Bührer c. Neonatology 2012.*

# CONCLUSIONES

- Para cierre del DAP, IBP oral parece ser tan eficaz como la indometacina IV y mas eficaz IBP ev.
- Perfil de seguridad comparable .
- Validez y generalización de los hallazgos están limitados por el tamaño de la muestra y calidad metodológica de los estudios incluidos.
- Falta de datos en RNPT extremos.

**Table 4.** Ongoing studies comparing oral ibuprofen to IV ibuprofen for PDA closure

Study	Population	Methods	Intervention	Outcomes	Expected date of completion
Su [27] Taiwan	GA <28 weeks with respiratory distress syndrome, PDA diagnosed by echocardiography	single-center, randomized controlled trial	oral ibuprofen (unspecified number of doses): initial dose 10 mg/kg, followed by 5 mg/kg at 24-h intervals as indicated by echocardiography IV ibuprofen (unspecified number of doses): initial dose 10 mg/kg, followed by 5 mg/kg at 24-h intervals as indicated by echocardiography	primary outcome: PDA closure secondary outcomes: adverse effects	June 2012
Erdeve et al. [28] Turkey	birth weight <1,000 g, PDA diagnosed by echocardiography	single-center, randomized controlled trial	oral ibuprofen (3 doses): initial dose 10 mg/kg, followed by 5 mg/kg at 24 and 48 h IV ibuprofen (3 doses): initial dose 10 mg/kg, followed by 5 mg/kg at 24 and 48 h	primary outcome: PDA closure secondary outcomes: adverse effects and renal tolerance	recruitment completed (April 2011)



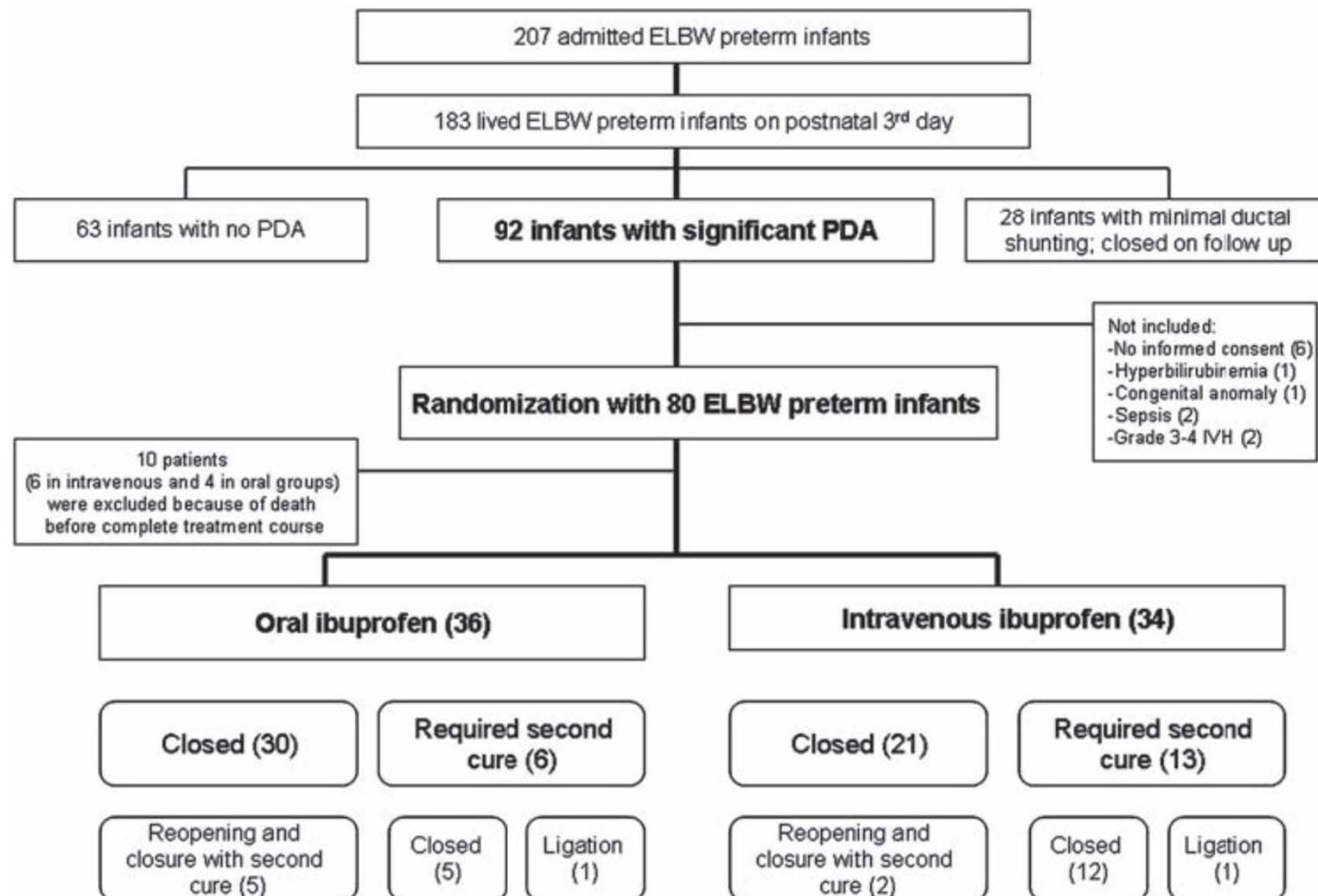
Original article

## Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants

Omer Erdeve,<sup>1</sup> Sadık Yurttutan,<sup>1</sup> Nahide Altug,<sup>2</sup> Ramazan Ozdemir,<sup>1</sup> Tulin Gokmen,<sup>1</sup> Ugur Dilmen,<sup>1</sup> Serife Suna Oguz,<sup>1</sup> Nurdan Uras<sup>1</sup>

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# OUTCOME PRIMARIO: CIERRE DUCTUS

- Cierre primario DAP : IBP oral 83,3% V/S 61,7% IBP ev .
- Necesidad de segundo curso de IBP fue similar en ambos grupos: 11/ 36 IBP oral V/S 15 / 34 IBP ev. ( mayor tasa de reapertura en el grupo oral).
- EG de los pacientes en que fracasa el primer curso de tratamiento : oral ( $26,4 \pm 1,1$  sem) V/S ev ( $26,3 \pm 1,2$  sem) .
- Las tasas de cierre acumulativos fueron altas en ambos grupos, y sólo un paciente cada uno de los grupos requirió tratamiento quirúrgico .

*Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants Omer Erdeve y Cols. Arch Dis Child Fetal Neonatal Ed 2012.*

**Table 2** Evaluation of renal function tests and bilirubin level after first course of treatment

Measurement	Intravenous ibuprofen			Oral ibuprofen			p*
	Before	After	p	Before	After	p	
Blood urea nitrogen (mg/dl)	79.3±28.4	79.9±37.2	0.91	61.8±33.9	65.2±31.7	0.53	0.07
Plasma creatinine (mg/dl)	0.79±0.27	0.76±0.22	0.64	0.68±0.24	0.69±0.26	0.96	0.16
Plasma bilirubin (mg/dl)	5.2±2.7	4.4±1.7	0.03	5.4±2.5	5.1±2.9	0.48	0.21
Plasma sodium (mmol/l)	140±6.4	138±6.9	0.05	140±6.5	137±7	0.12	0.95
Urine output (ml/kg/h)	3.2±1	2.8±0.8	0.06	2.9±0.7	3±0.7	0.44	0.39

\*p value for after treatment measurements between groups.

- No se encontraron diferencias estadísticamente significativas entre IBP oral y ev en repercusión de la función renal .
- No se registran casos de insuficiencia renal .
- Se recomienda control de la función renal y evitar uso de fármacos potencialmente nefrotóxicos en pacientes tratados con ibuprofeno.

*Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants Omer Erdeve y Cols. Arch Dis Child Fetal Neonatal Ed 2012.*

**Table 3** Safety outcomes and adverse events after oral and intravenous treatments

	Oral (n=36)	IV (n=34)	p
Duration of hospitalisation, mean±SD (days)	73.7±24.2	79.6±21.4	0.28
Necrotising enterocolitis, n (%)	2(5.6)	3(8.8)	0.59
Spontaneous intestinal perforation, n (%)	–	1 (2.9)	0.30
Gastrointestinal bleeding, n (%)	–	–	–
Sepsis, n (%)	11(30.6)	17(50)	0.09
Duration n-CPAP, median (range) (days)	5 (0–25)	5 (0–30)	0.64
Duration mechanical ventilator, median (range) (days)	2 (0–25)	3 (0–25)	0.09
Increase in the grade of intraventricular haemorrhage, n (%)	5 (13.9)	4 (11.8)	0.79
Pneumothorax, n (%)	2 (5.6)	2 (5.9)	0.95
Pulmonary haemorrhage, n (%)	–	3 (8.8)	0.07
Pulmonary hypertension	–	–	–
Chronic lung disease *, n (%)	17 (47.2)	19 (55.9)	0.46
Postnatal steroid use for severe chronic lung disease, n (%)	8 (22.2)	17 (50)	0.01
ROP required laser treatment†, n (%)	5 (12.9)	6 (17.6)	0.64
Death, n (%)	2 (5.6)	1 (2.9)	0.58

- No se registro sangrado gastrointestinal y sólo un paciente presento perforación intestinal espontanea .
- NEC : 5,6% IBP oral V/S 8,8% IBP ev .
- Necesidad de corticoides a las 36 sem fue menor en grupo IBP oral.

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- Días de hospitalización, CPAP, VMI : sin diferencias.
- Sepsis, EPC y ROP : < con IBP oral , diferencias no fueron estadísticamente significativas.
- HIV: > con IBP oral pero diferencias no fueron estadísticamente significativas.

*Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants Omer Erdeve y Cols. Arch Dis Child Fetal Neonatal Ed 2012.*

# CONCLUSIONES

- Eficacia en cierre de DAP en RNPT MBPN , de IBP oral es similar a IBP ev.
- En este trabajo no se encontraron diferencias estadísticamente significativas entre IBP oral y ev en repercusión función renal, complicaciones gastrointestinales, sepsis, EPC y ROP ,HIV.
- Considerar las limitaciones del estudio : tamaño de la muestra y ausencia de ciego completo.

*Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants Omer Erdeve y Cols. Arch Dis Child Fetal Neonatal Ed 2012.*

# Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review)

Ohlsson A, Walia R, Shah SS



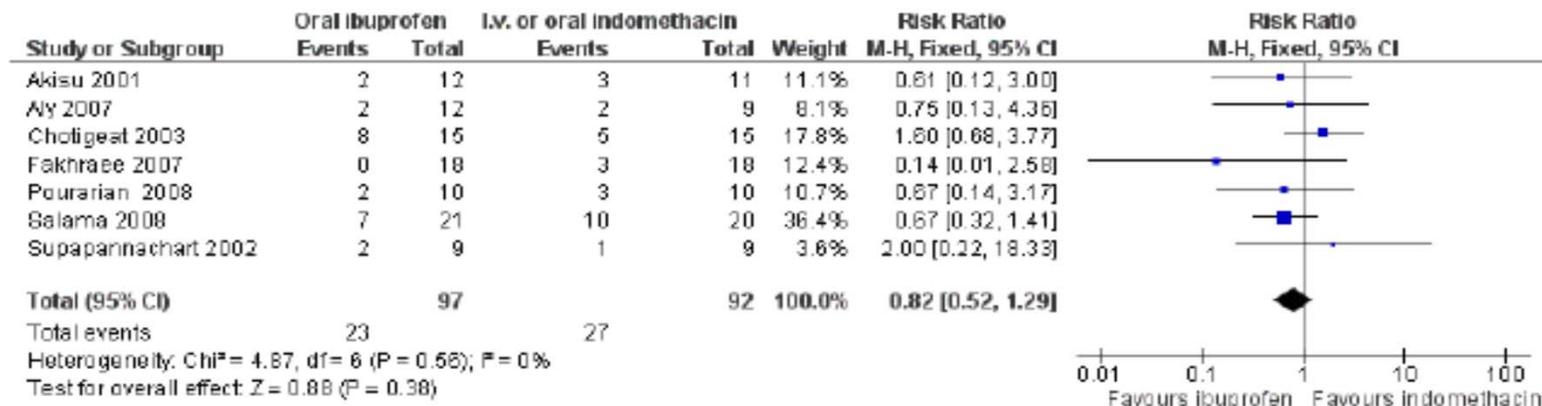
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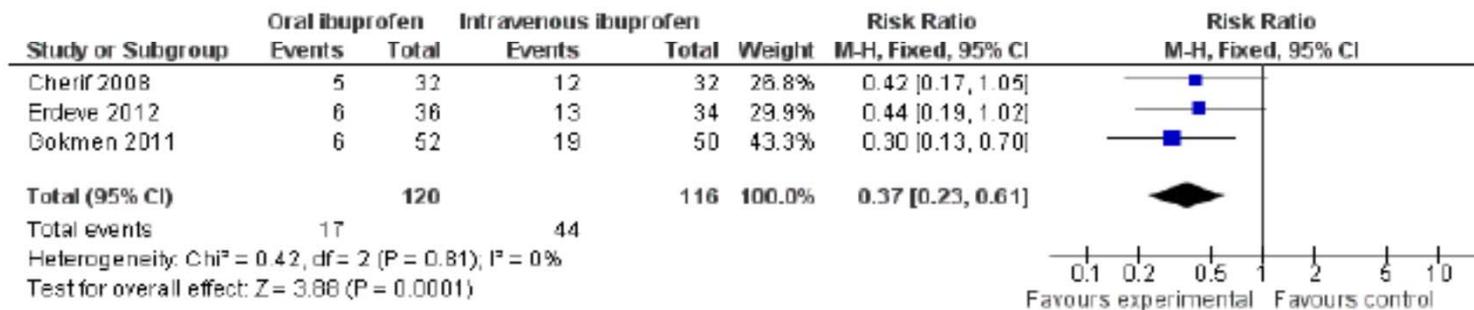
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# FRACASO EN CIERRE DAP

**Figure 3. Forest plot of comparison: 4 Oral ibuprofen versus iv or oral indomethacin, outcome: 4.1 Failure to close a PDA (after three doses).**



**Figure 5. Forest plot of comparison: 5 Oral ibuprofen versus iv ibuprofen, outcome: 5.1 Failure to close a PDA (after single or three doses).**



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

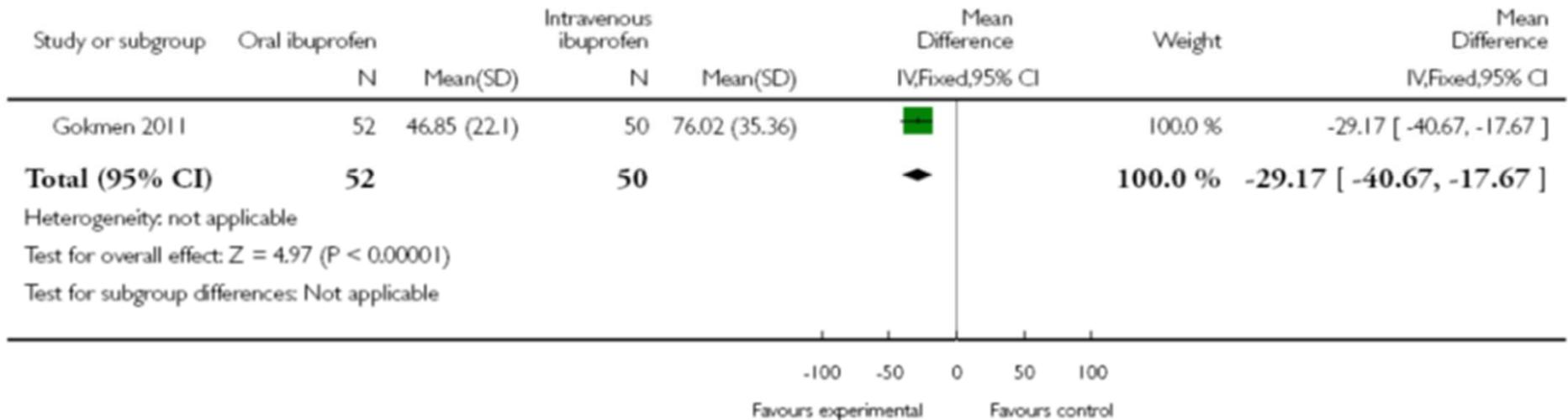
# EFFECTOS RENALES

## Analysis 5.22. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 22 Serum/plasma creatinine levels (micromol/L) after treatment.

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 22 Serum/plasma creatinine levels (micromol/L) after treatment



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

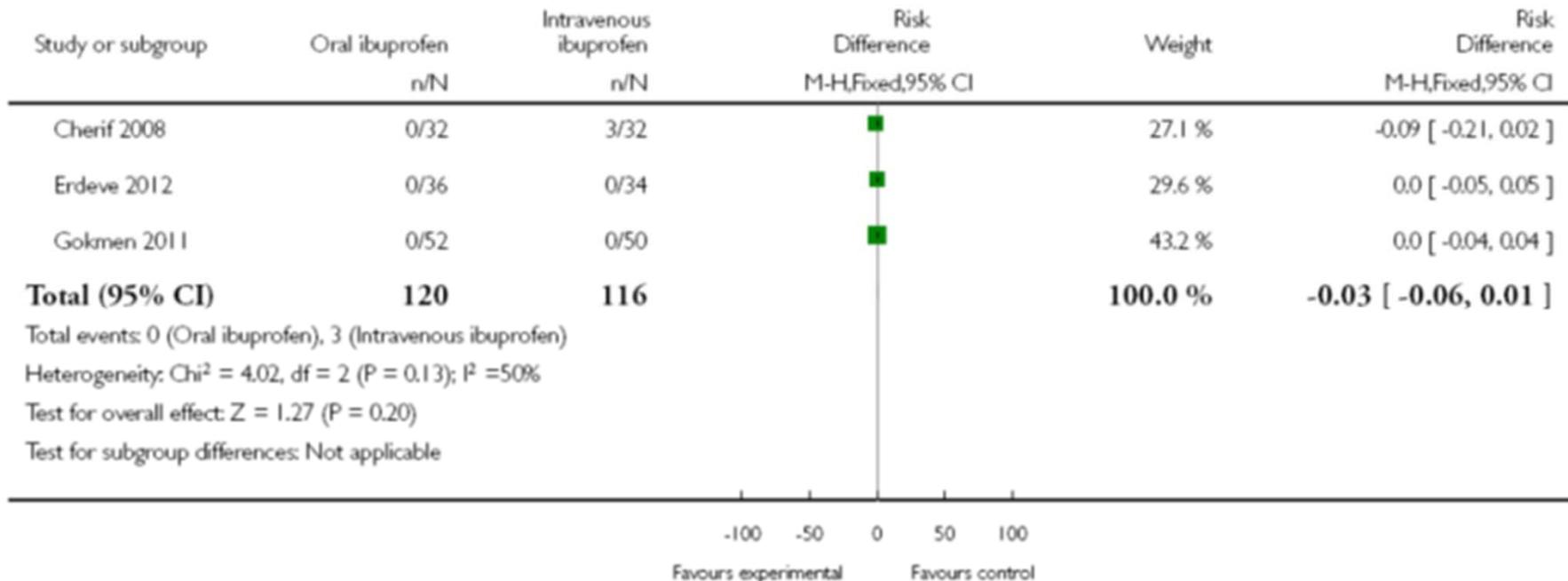
# EFFECTOS RENALES

## Analysis 5.23. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 23 Oliguria (< 1 cc/kg/hr).

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 23 Oliguria (< 1 cc/kg/hr)



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

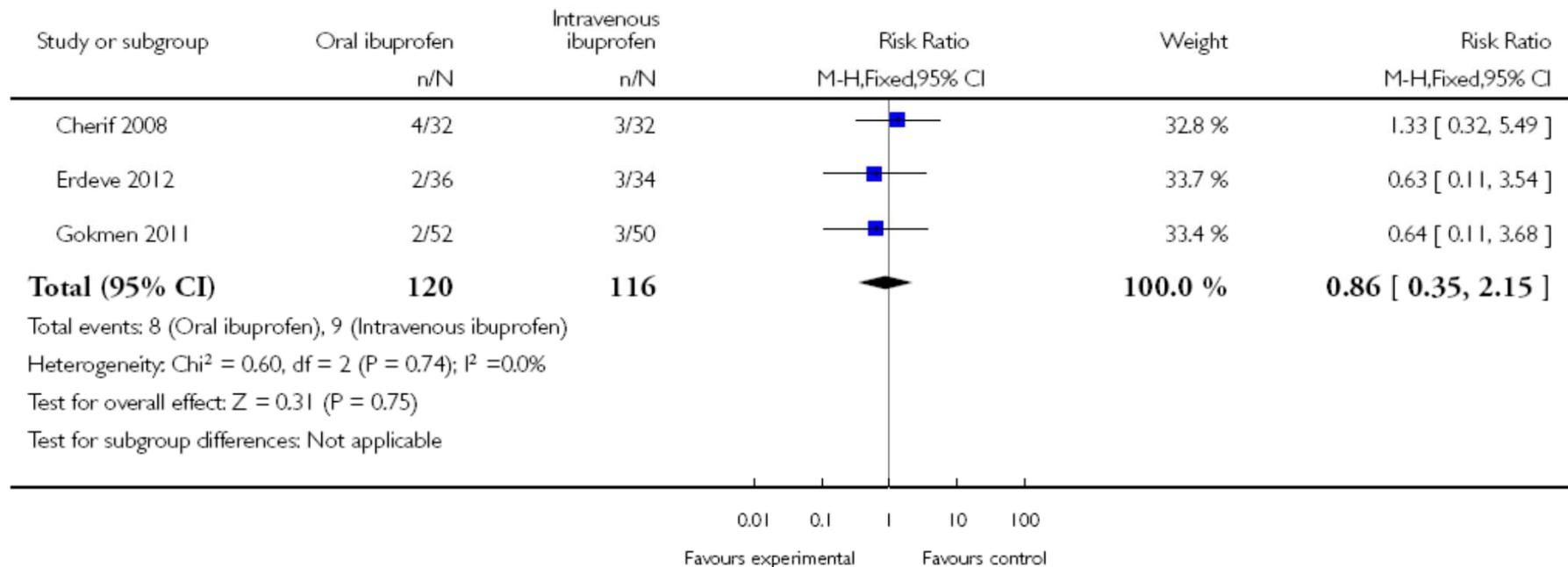
# EFFECTOS GASTROINTESTINALES:NEC

## Analysis 5.17. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 17 Necrotising enterocolitis (any stage).

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

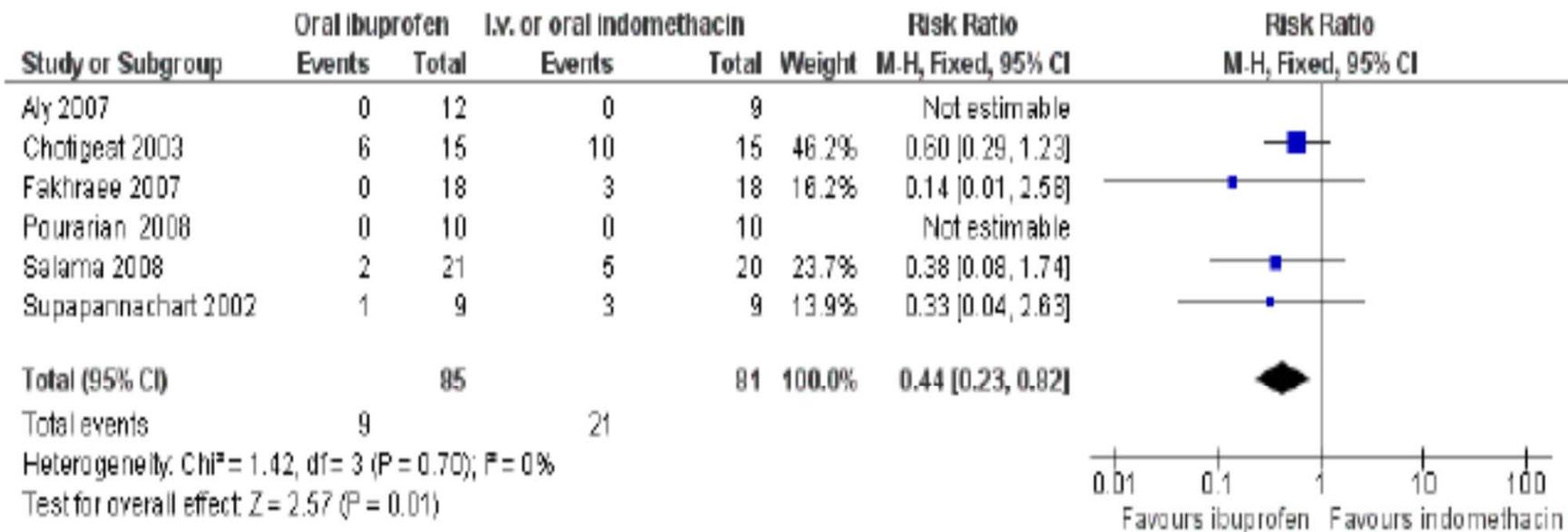
Outcome: 17 Necrotising enterocolitis (any stage)



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants.  
(Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

# EFFECTOS GASTROINTESTINALES:NEC

Figure 4. Forest plot of comparison: 4 Oral ibuprofen versus iv or oral indomethacin, outcome: 4.18 Necrotizing enterocolitis (any stage).



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

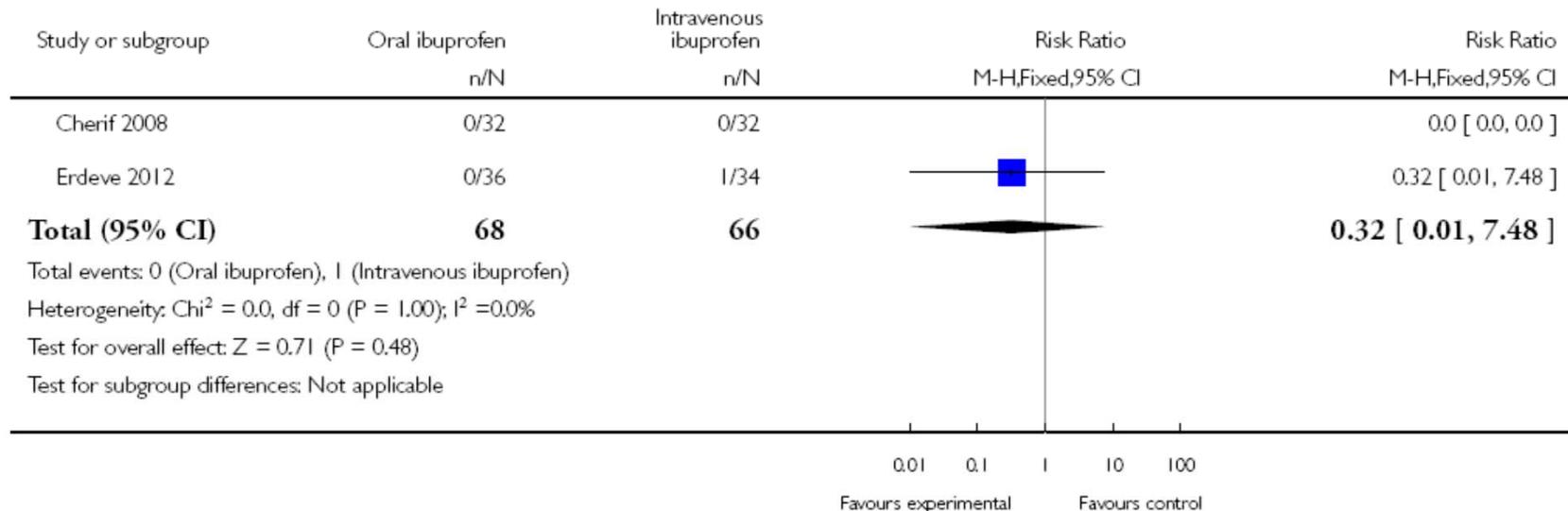
# EFECTOS GASTROINTESTINALES : PERFORACION INTESTINAL

## Analysis 5.18. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 18 Intestinal perforation.

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 18 Intestinal perforation



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

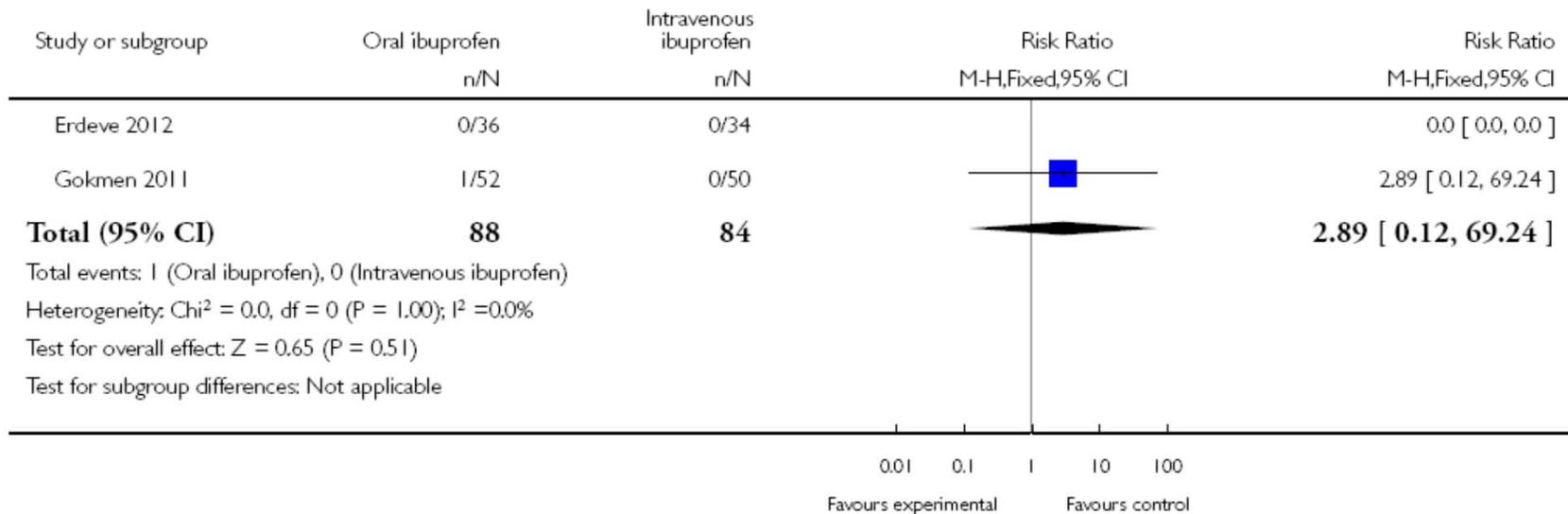
# EFFECTOS GASTROINTESTINALES: HEMORRAGIA DIGESTIVA

## Analysis 5.19. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 19 Gastrointestinal bleed.

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 19 Gastrointestinal bleed



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

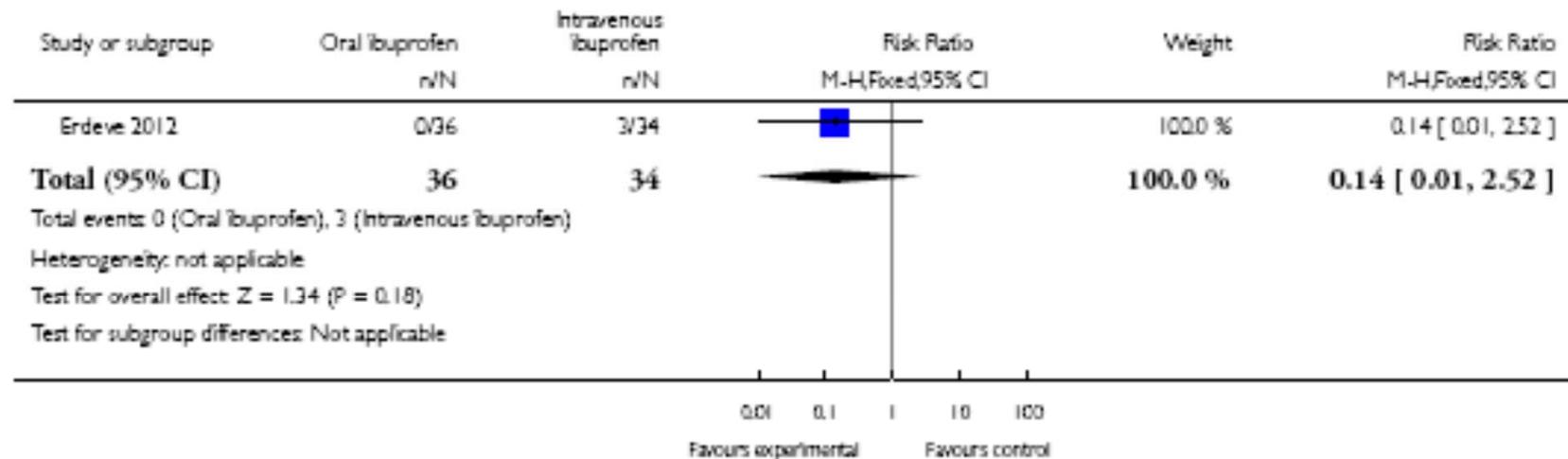
# EFFECTOS PULMONARES: HEMORRAGIA PULMONAR

## Analysis 5.9. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 9 Pulmonary haemorrhage.

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 9 Pulmonary haemorrhage



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

# EFECTOS PULMONARES: HIPERTENSION PULMONAR

## Analysis 5.10. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 10 Pulmonary hypertension.

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 10 Pulmonary hypertension

Study or subgroup	Oral ibuprofen	Intravenous ibuprofen	Risk Ratio	
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
Erdevi 2012	0/36	0/34		0.0 [ 0.0, 0.0 ]
Gokmen 2011	0/52	0/50		0.0 [ 0.0, 0.0 ]
<b>Total (95% CI)</b>	<b>88</b>	<b>84</b>		<b>0.0 [ 0.0, 0.0 ]</b>

Total events: 0 (Oral ibuprofen), 0 (Intravenous ibuprofen)  
Heterogeneity: Chi<sup>2</sup> = 0.0, df = 0 (P<0.00001); I<sup>2</sup> = 0.0%  
Test for overall effect: Z = 0.0 (P < 0.00001)  
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100  
Favours experimental Favours control

Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

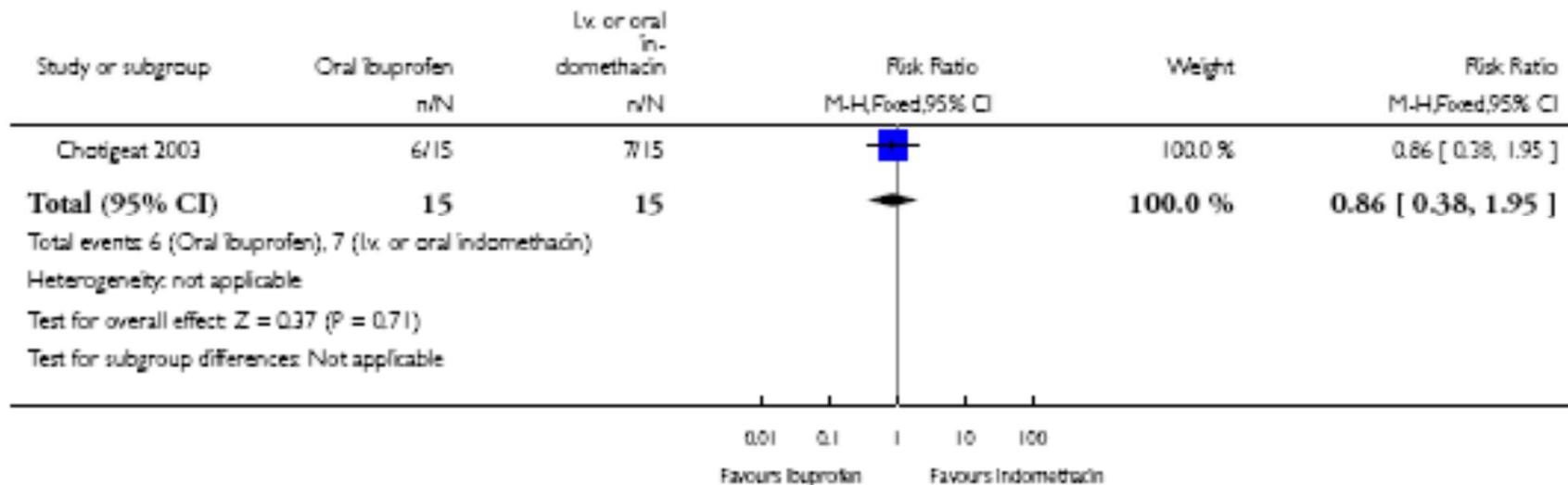
# EFFECTOS PULMONARES: EPC

## Analysis 4.8. Comparison 4 Oral ibuprofen versus iv or oral indomethacin, Outcome 8 Chronic lung disease (at 28 days).

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 4 Oral ibuprofen versus iv or oral indomethacin

Outcome: 8 Chronic lung disease (at 28 days)



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

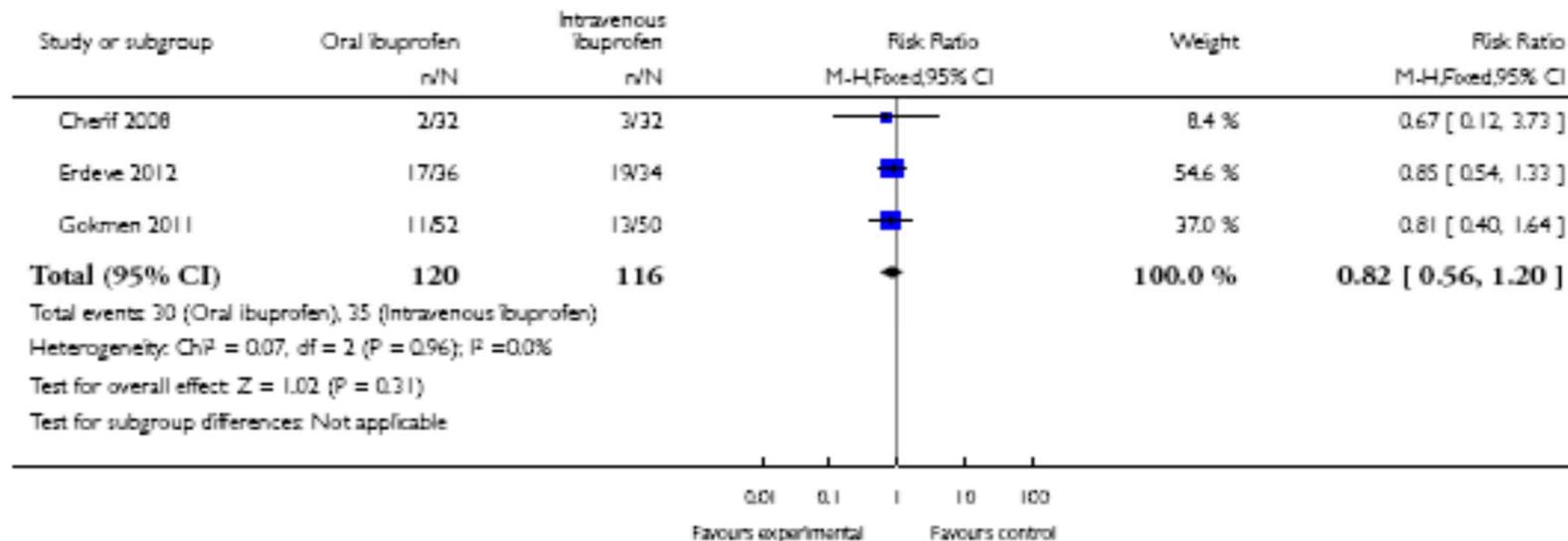
# EFFECTOS PULMONARES: EPC

## Analysis 5.12. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 12 Chronic lung disease (at 36 weeks postmenstrual age or at discharge).

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 12 Chronic lung disease (at 36 weeks postmenstrual age or at discharge)



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

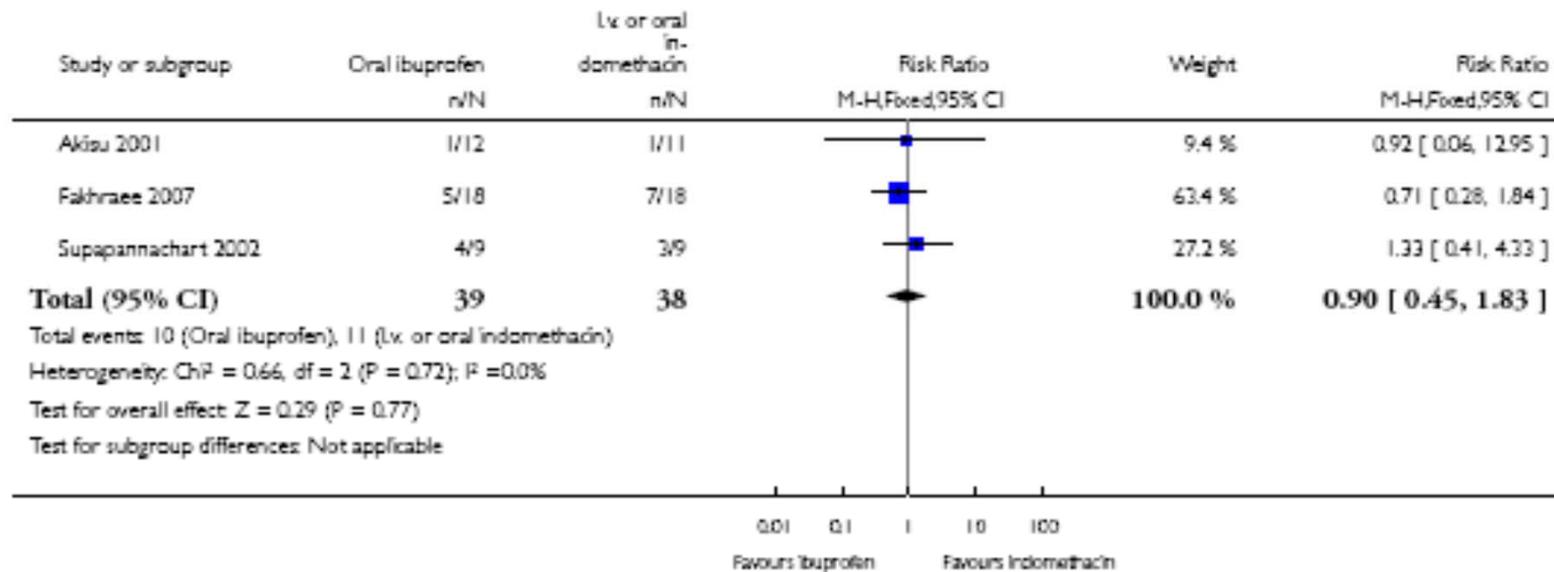
# EFFECTOS NEUROLOGICOS

## Analysis 4.11. Comparison 4 Oral ibuprofen versus iv or oral indomethacin, Outcome 11 Intraventricular haemorrhage (grades I-IV).

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 4 Oral ibuprofen versus iv or oral indomethacin

Outcome: 11 Intraventricular haemorrhage (grades I-IV)



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

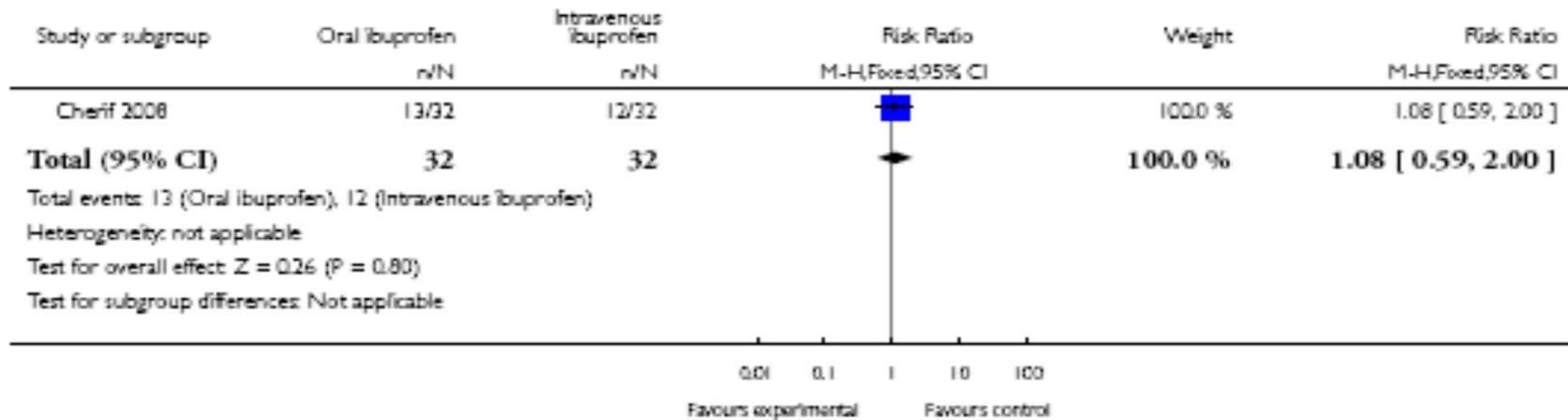
# EFFECTOS NEUROLOGICOS

## Analysis 5.14. Comparison 5 Oral ibuprofen versus iv ibuprofen, Outcome 14 Intraventricular haemorrhage (grades I-IV).

Review: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 5 Oral ibuprofen versus iv ibuprofen

Outcome: 14 Intraventricular haemorrhage (grades I-IV)



Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review) Ohlsson A, Walia R, Shah SS. The Cochrane Collaboration 2013 .

# Intravenous Paracetamol Treatment in the Management of Patent Ductus Arteriosus in Extremely Low Birth Weight Infants

Mehmet Yekta Oncel<sup>a</sup> Sadik Yurttutan<sup>a</sup> Halil Degirmencioglu<sup>a</sup> Nurdan Uras<sup>a</sup>

Neonatology 2013;103:166–169

- RNPT con DAPHS con contraindicación para alimentación o intolerancia alimentaria .
- DAPHS : clínica sugerente y ecocardiografía .
- Paracetamol ev: 15 mg/kg cada 6 hrs , ECO 3° día de tratamiento. Si Fracasa , se extiende por 6 días.
- Se midieron enzimas hepáticas pre-y post tratamiento y niveles de paracetamol diarios durante 3 días consecutivos.

**Table 1.** Clinical characteristics, echocardiographic findings and morbidities of the study population

Case No.	Gestational age, weeks	Birth weight g	Age paracetamol begun, days	PDA diameter mm	LA:Ao ratio	Reason for not using NSAIDs	Posttreatment PDA status	Proven sepsis	NEC (grade III-IV)	ROP	CLD	Death
1	28	640	8	3.0	2.1	FI	closed with single course	-	-	-	-	-
2	25 <sup>2/7</sup>	740	12	2.0	1.6	FC	closed with single course	+	-	+	+	-
3	25	590	3	1.5	1.8	FI and hyperbilirubinemia	closed with single course	+	-	-	-	+
4	27 <sup>5/7</sup>	930	15	2.2	2.0	FC	closed with extended course	-	-	-	-	-
5	24	730	3	2.0	1.6	FI and hyperbilirubinemia	closed with single course	-	-	+	+	-
6	27 <sup>1/7</sup>	880	5	1.8	2.0	FI	closed with single course	-	-	-	-	-
7	28 <sup>3/7</sup>	910	7	2.5	2.0	FI	closed with single course	-	-	-	-	-
8	27 <sup>4/7</sup>	810	5	1.7	1.9	FC	closed with extended course	-	-	-	-	-
9	29	990	10	2.4	2.2	FI	closed with single course	-	-	-	-	-
10	26	720	2	2.0	1.8	FC and hyperbilirubinemia	closed with extended course	-	-	-	+	-

NSAIDs = Non-steroidal anti-inflammatory drugs; FI = feeding intolerance; FC = feeding contraindicated [meconium ileus or suspected necrotizing enterocolitis (NEC)]; ROP = retinopathy of prematurity (required laser treatment); CLD = chronic lung disease.

- 10 RNPT : masc. 40% y fem. 60% ,EG 27+4 sem y PN 775 grs .
- Cierre exitoso de DAPHS en todos los pacientes.
- 70% responde a ciclo único, 30% tratamiento extendido.
- Niveles de paracetamol normales en todos los pacientes.
- Enzimas hepáticas pre-post tto normales en todos los pacientes.
- No se atribuyen efectos secundarios al uso de paracetamol ev .

*Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants.Mehmet Yekta Oncel y Cols .Neonatology 2013.*

# PARACETAMOL :MECANISMO ACCION

- Mecanismo de acción del paracetamol es controversial.
- COX tiene 2 zonas catalíticas: ciclooxigenasa y peroxidasa.
- AINES inhiben la ciclooxigenasa , pero no la actividad peroxidasa de la enzima.
- Paracetamol actuaría inhibiendo la actividad peroxidasa de COX.

*Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants.Mehmet Yekta Oncel y Cols .Neonatology 2013.*

# CONCLUSIONES

- IBP oral ha demostrado ser tan eficaz como IBP ev e indometacina para cierre de DAP en RNPT.
- Perfil de seguridad y efectos adversos son comparables a ibuprofeno endovenoso.
- IBP oral se podría considerar como una opción segura y eficaz para el manejo del DAP en RNPT .
- Con respecto a uso de paracetamol falta evidencia que permita recomendar su uso.

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*Gracias.*