Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis

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ABSTRACT

Objectives We performed a systematic review and meta-analysis of all the available evidence to assess the efficacy and safety of paracetamol for the treatment of patent ductus arteriosus (PDA) in neonates, and to explore the effects of clinical variables on the risk of closure.

Data source MEDLINE, Scopus and ISI Web of Knowledge databases, using the following medical subject headings and terms: paracetamol, acetaminophen and patent ductus arteriosus. Electronic and manual screening of conference abstracts from international meetings of relevant organisations. Manual search of the reference lists of all eligible articles.

Study selection Studies comparing paracetamol versus ibuprofen, indomethacin, placebo or no intervention for the treatment of PDA.

Data extraction Data regarding efficacy and safety were collected and analysed.

Results Sixteen studies were included: 2 randomised controlled trials (RCTs) and 14 uncontrolled studies. Quality of selected studies is poor. A meta-analysis of RCTs does not demonstrate any difference in the risk of ductal closure (Mantel–Haenszel model, RR 1.07, 95% CI 0.87 to 1.33 and RR 1.03, 95% CI 0.92 to 1.16, after 3 and 6 days of treatment, respectively). Proportion meta-analysis of uncontrolled studies demonstrates a pooled ductal closure rate of 49% (95% CI 29% to 69%) and 76% (95% CI 61% to 88%) after 3 and 6 days of treatment with paracetamol, respectively. Safety profiles of paracetamol and ibuprofen are similar.

Conclusions Efficacy and safety of paracetamol appear to be comparable with those of ibuprofen. These results should be interpreted with caution, taking into account the non-optimal quality of the studies analysed and the limited number of neonates treated with paracetamol so far.

What is already known on this topic?

- Paracetamol has been proposed for the treatment of patent ductus arteriosus in preterm neonates.
- Ibuprofen and indomethacin are the first choice for the treatment of patent ductus arteriosus in preterm neonates.

What this study adds?

- Meta-analysis of controlled and uncontrolled studies demonstrated an efficacy of paracetamol comparable with that reported for ibuprofen.
- Efficacy of paracetamol seems to depend on gestational age and postnatal age of neonate and on modalities of drug administration.

INTRODUCTION

A persistent patent ductus arteriosus (PDA) has significant clinical consequences, and is a main factor affecting the survival rate of preterm neonates.[1 2] A prompt ductal closure is crucial to reduce morbidity and mortality in this particular population. Pharmacological treatment with ibuprofen and indomethacin is the first therapeutic choice for PDA.[3 4] By inhibiting the cyclo-oxygenase (COX) component of prostaglandin-H_2 synthase (PGHS), these two drugs reduce the levels of circulating prostaglandins, on which depends the persistency of ductus arteriosus in the first period of life.[5] Recent studies have shown that paracetamol, an inhibitor of the peroxidase component of PGHS,[6] may be considered as an alternative drug for the treatment of PDA.[7–22] However, many aspects regarding paracetamol use for ductal closure in preterm neonates, such as efficacy in extremely preterm and low birthweight (BW) infants, safety profile, optimal dose, timing of the first dose and route of administration remain largely unexplored. Thus, to address these issues, we performed a systematic review and meta-analysis of the evidence available in the literature. In particular, we systematically reviewed and analysed controlled and uncontrolled studies to compare the efficacy of paracetamol with other COX inhibitors (COX-i) and explore the influence of different variables on the probability of ductal closure.

METHODS

In compliance with PRISMA guidelines, we performed a systematic review and meta-analysis of the studies published.[23] The study was approved by the

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Ethics Committee of 'La Sapienza' University in Rome (n. 13409).

Eligibility criteria

We considered eligible all studies fulfilling the following criteria:

1. studies of any design including controlled and uncontrolled trials, such as randomised controlled trials (RCTs), open trials, retrospective studies, case series and case reports, published until November 2014;
2. studies including preterm neonates (gestational age (GA) at birth <37 weeks) who received pharmacological treatment for haemodynamically significant PDA (defined by echocardiographic examination) regardless of their postnatal age;
3. studies in which the intervention applied was paracetamol given for PDA closure versus COX-i or placebo or no intervention; studies in which paracetamol was not used for the purpose of PDA closure were excluded.

Outcomes

The main outcome was PDA closure. Secondary outcomes were mortality during hospital stay, morbidity during hospital stay (ie, intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity) and reopening of the ductus arteriosus.

We also investigated the safety profile of PDA treatment (ie, gastrointestinal bleeding, liver, haematopoietic or renal toxicity, hypersensitivity reactions, skin reactions, hypotension and hypothermia). All dichotomous outcomes were measured as number of patients with the event divided by the total number of patients who had received any kind of intervention.

Search strategy

A standard systematic review technique was adopted.[24] We conducted electronic searches in MEDLINE, Scopus and ISI Web of Knowledge databases, with no language restriction, using the following medical subject headings and terms: paracetamol, acetaminophen and patent ductus arteriosus. Electronic and manual screening of conference abstracts from international meetings of relevant organisations (Pediatric Academic Societies and European Society for Paediatric Research and Perinatal Society of Australia and New Zealand) was also performed. Finally, we made a manual search of the reference lists of all eligible articles.

Study selection

Three authors independently assessed study eligibility for inclusion according to pre-established criteria. We used a specifically designed form to include or exclude the studies identified. An accurate check to exclude duplicate publications was performed. Corresponding authors were contacted when the eligibility criteria of their papers were unclear. Differences in opinion were resolved after discussion between the researchers to achieve consensus.

Data extraction

Three authors independently extracted the data from the selected articles using a specifically designed form. For each selected study, the form summarised data on authorship, year of publication, study design, number of patients enrolled, postnatal age, GA and BW of the patients enrolled in each treatment group for each study, presence of a control group (ie, COX-i, placebo or no intervention), criteria used to diagnose PDA, timing of paracetamol use (ie, paracetamol given as first-line therapy or after COX-i), dosing regimen used, closure of ductus after any treatment (ie, the number of patients with closure of PDA divided by the total number of patients who had received any kind of intervention in each study), occurrence of reopening (ie, the number of patients with echocardiographic evidence of closure after any treatment followed by reopening of PDA on the total number of patients experiencing ductal closure in each treatment group of each study), morbidity (ie, the number of patients with morbidities on total number of neonates in each treatment group of each study), mortality (ie, the number of non-survival patients on total number of neonates in each treatment group in each study), occurrence of adverse events and side effects specifically associated with pharmacological treatment of PDA (ie, the number of patients with adverse events or side effects on total number of neonates in each treatment group in each study).

The authors of the studies selected were contacted and invited to supply line-by-line raw data for each individual patient. These data were checked for missing information, errors and inconsistencies with published reports. The data extracted were compared for any difference. If evidenced, differences were resolved by discussion and consensus between researchers.

Risk of bias

For controlled studies, we assessed selection bias (random sequence generation and allocation concealment), performance bias (blinding of the study personnel as to which intervention a neonate had received), detection bias (blinding of personnel evaluating outcomes), attrition bias (completeness of reporting data, reason and balance across groups of missing data), reporting bias (reporting of the study's prespecified or expected outcomes of interest to the review) and other source of bias (early interruption of the trial due to data-dependent process or bias related to the specific study design). We categorised for each study the risks of bias as high, low or unclear, using standard methods.[24]

For uncontrolled studies, randomisation and allocation bias could obviously not be evaluated. For these studies, we judged the risk of selection bias as low or high if patients had been enrolled or not enrolled as consecutively observed based on a pre-existent study protocol and if numbers and reasons for possible exclusions were reported or not reported specifically. Selection bias was judged as unclear when these aspects were not evaluable. Performance bias, detection bias, attrition bias and other sources of bias were evaluated using the criteria previously described.

The risk of bias was assessed independently by three researchers using a specific form. Differences in opinion were resolved by discussion and consensus. The corresponding authors of selected studies were contacted when information useful to assess the risks of bias was unclear or missing in their manuscripts as published.

Statistics

For RCTs, we used the Mantel–Haenszel method for calculating the weighted summary risks. To measure the heterogeneity, we used Cochran's Q test. Homogeneity between studies was assessed using I^2 statistic. Fixed effect meta-analysis models were used when there was minimal evidence of heterogeneity, while random effect models were used if the I^2 value was >30% for effect estimates.[24] The p value cut-off used for the test of heterogeneity was <0.1. We reported dichotomous outcome data using relative risk (RR) with respective 95% CI. Analyses were performed on an intention-to-treat basis (ITT). Missing data were dealt with by using the last available

measurement for each individual at the time point prior to withdrawal from the study.

For uncontrolled studies, we used proportion meta-analysis to measure outcomes by calculating proportions and 95% CI for each study and then pooled the data to derive a pooled proportion and 95% CI.[25] The impact of heterogeneity on the pooled estimates of the individual outcomes of the meta-analysis was assessed with the Cochran Q statistic and I^2 statistic. As the Cochran Q test has a low sensitivity for detecting heterogeneity, a p value of 0.1 was considered significant for the presence of statistical heterogeneity. Fixed effect meta-analysis models were used when there was minimal evidence of heterogeneity, while random effect models were used if the I^2 value was >30% for effect estimates.

We planned to perform a subgroup analysis to determine efficacy of drugs for PDA in relation to GA (<28 and ≥28 weeks), BW (<1000 and ≥1000 g), postnatal age (≤7 and >7 days), dose (low (≤45 mg/Kg/day) or high (>45 mg/Kg/day)), route of administration (oral or intravenous), timing of paracetamol use (as first-line therapy or after failure of COX-i). For subgroup analyses, the weighted results were calculated separately in every subgroup, and were then compared with χ^2 tests.

A sensitivity analysis was planned to determine if the findings would be affected by including only studies with low selection bias.

We reported efficacy after 3 and 6 days of treatment from the enrolment and secondary outcomes at the end of hospitalisation period because negative consequences of PDA treatment failure were usually observed only after several days.

Statistics were performed using StatsDirect V.2.8.0 and IBM SPSS Statistics V.22 softwares.

RESULTS

Studies' characteristics

We selected 16 studies as indicated in figure 1. The main characteristics of the selected studies, two RCTs[21 22] and 14 uncontrolled studies,[7–20] are reported in tables 1 and 2, respectively. We received additional information and raw data for each individual patient from the corresponding authors of 15 of the 16 studies selected.[7–20 22] Dang *et al*[21] did not provide additional information, and the data of this study were analysed as published.

Risk of bias

Risks of bias for the two RCTs are reported in table 3. We judged the risk of selection bias as high in all uncontrolled studies.[7 12–16] In all 14 uncontrolled studies, any blinding method was adopted. Attrition bias was judged as low for all 14 studies. Other sources of bias were not clearly evaluable for all 14 uncontrolled studies.

Outcomes

Evidence from randomised controlled studies

Pooled results from the two RCTs showed no difference in PDA closure for paracetamol compared, with ibuprofen, after 3 and 6 days of treatment (figures 2 and 3). The data available were not suitable for subgroup and sensitivity analyses.

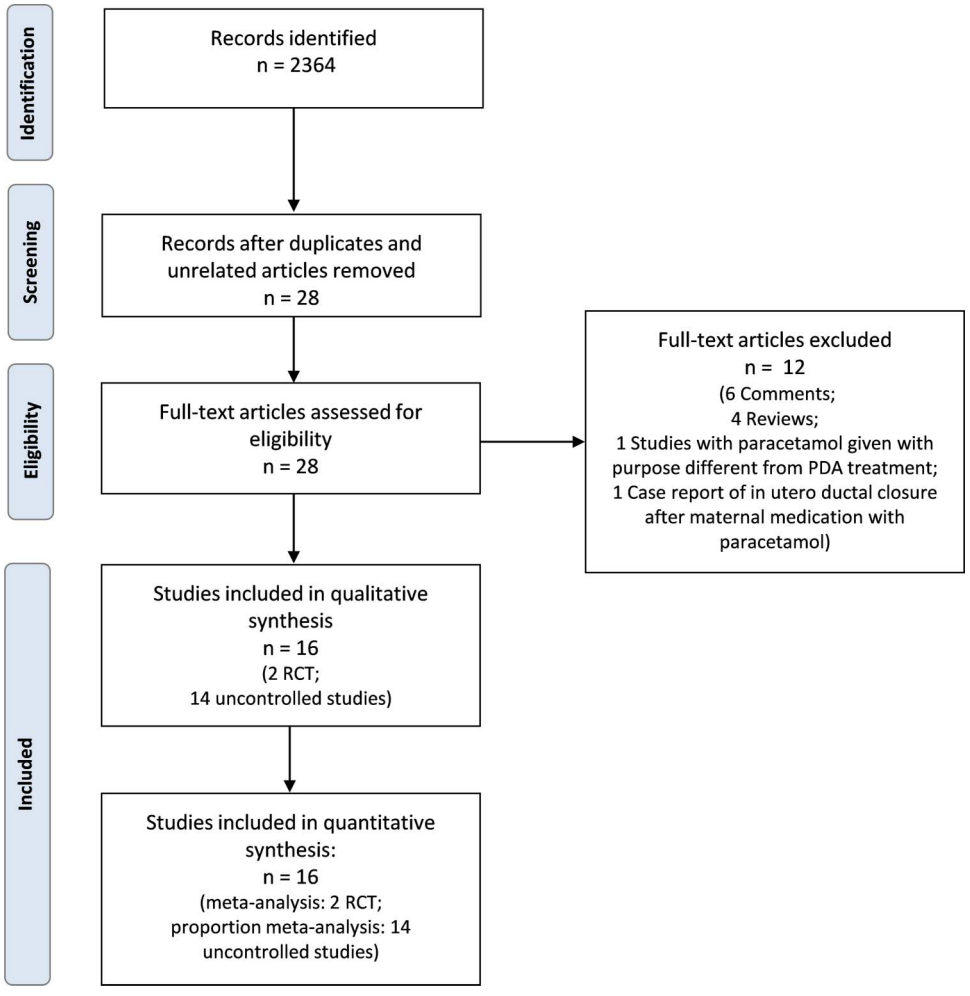

Figure 1 PRISMA flow chart. PDA, patent ductus arteriosus; RCT, randomised controlled trial.

Table 1 Characteristics of randomised controlled trials

Authors Publication year	Sample size	Birth weight*, g	Gestational age*, weeks	Postnatal age, days	Echocardiographic criteria defining hs-PDA	Route	Dose, mg/kg/die	Timing
Dang *et al* 2013[21]	P: 80 I: 80	P:1592 (349) I: 1531 (453)	P: 31.2 (1.8) I: 30.9 (2.2)	0–14	Ductal diameter LA: Ao root ratio Reverse diastolic flow in Ao Left ventricular enlargement	P: oral I: oral	P: 60 I: 10-5-5	First-line therapy
Oncel *et al* 2014[22]	P: 45 I: 45	P: 929 (224) I: 974 (249)	P: 27.5 (2.1) I: 27.3 (2.2)	2–4	Ductal diameter LA: Ao root ratio Reverse diastolic flow in Ao Poor cardiac function	P: oral I: oral	P: 60 I: 10-5-5	First-line therapy

*Data are expressed as mean (SD).
Ao, aorta. I, ibuprofen; hs-PDA, haemodinamically significant patent ductus arteriosus; LA, left atrium; P, paracetamol.

Table 2 Characteristics of uncontrolled studies

Authors Publication year	Sample size	Birth weight*, g	Gestational age*, weeks	Postnatal age*, days	Echocardiographic criteria defining hs-PDA	Route	Dose, mg/kg/die	Timing
Alan *et al* 2013[12]	3	840 (810–1240)	26 (26–33)	9 (8–19)	Ductal diameter, LA:Ao root ratio, ductus arteriosus:birth weight ratio	Intravenous	60	After COX-i failure
El-Khuffash *et al* 2014[19]	21	790 (530–1200)	25 (24–28)	25 (3–56)	Ductal diameter, plus pulmonary overcirculation or systemic hypoperfusion	9 intravenous 12 oral	60	16 after COX-i failure 5 first-line therapy
Hammerman *et al* 2011[7]	5	935 (720–1210)	26 (26–29)	10 (3–17)	Ductal diameter, LA:Ao root ratio, gradient across PDA, reverse diastolic flow in Ao, ductus diameter:aorta ratio	Oral	60	2 after COX-i failure 3 first-line therapy
Jasani *et al* 2013[15]	6	1107 (1040–1234)	29 (28–31)	5.5 (3–10)	Ductal diameter, LA:Ao root ratio	Oral	60	4 after COX-i failure 2 first-line therapy
Kessel *et al* 2014[16]	7	991 (789–1322)	28 (26–30)	6 (2–27)	LA:Ao root ratio, left ventricular and left atrial enlargement, moderate left-to-right PDA flow, plus ventilation	Oral	60	2 after COX-i failure 5 first-line therapy
Nadir *et al* 2014[18]	7	853 (656–951)	26 (24–27)	5 (2–22)	Ductal diameter, plus ventilation or feeding intolerance	Oral	60	3 after COX-i failure 4 first-line therapy
Oncel *et al* 2013[8]	8	995 (630–2970)	28 (23–36)	9.5 (5–27)	Ductal diameter, LA:Ao root ratio, reverse diastolic flow in Ao, poor cardiac function, plus clinical symptoms	Oral	60	6 after COX-i failure 2 first-line therapy
Oncel *et al* 2013[9]	10	775 (590–990)	27 (24–29)	6 (2–15)	Ductal diameter, LA:Ao root ratio, reverse diastolic flow in Ao, left-to-right shunting of blood	Intravenous	60	First-line therapy
Ozdemir *et al* 2013[14]	7	820 (620–1615)	25 (23–32)	35 (20–47)	Ductal diameter, LA:Ao root ratio, reverse diastolic flow in Ao, left ventricular enlargement	Oral	60	After COX-i failure
Roofthooft *et al* 2013[13]	10	700 (365–950)	25 (23–26)	22 (13–30)	Ductal diameter, LA:Ao root ratio, pattern of diastolic flow in Ao, flow on ductus, LPA end diastolic flow	9 intravenous 1 oral	60	6 after COX-i failure 4 first-line therapy
Sinha *et al* 2013[11]	10	995 (800–1380)	29 (27–33)	5 (4–7)	Ductal diameter, LA:Ao root ratio, left-to-right shunting of blood, mean pulmonary arterial pressure, peak systolic pulmonary arterial pressure	Oral	45	First-line therapy
Tekgunduz *et al* 2014[20]	13	950 (470–1390)	29 (24–31)	3 (2–9)	Ductal diameter, LA:Ao root ratio	Intravenous	30–60	First-line therapy
Terrin *et al* 2014[17]	8	700 (530–930)	26 (23–29)	2 (2–5)	Ductal diameter, LA:Ao root ratio, reverse or absent diastolic flow in Ao, unrestrictive pulsatile transductal flow	Intravenous	30–60	First-line therapy
Yurttutan *et al* 2013[10]	6	1260 (920–1600)	28 (26–32)	4 (3–7)	Ductal diameter, LA:Ao root ratio, reverse diastolic flow in Ao, left-to-right shunting of blood, poor cardiac function	Oral	60	First-line therapy

*Data are expressed as median (min–max).
Ao, aorta; COX-i, cyclo-oxygenase inhibitor; hs-PDA, haemodinamically significant patent ductus arteriosus; LA, left atrium; LPA, left pulmonary artery.

Table 3 Risk of bias in randomised controlled trials

	Selection bias I (random sequence generation)	Selection bias II (allocation concealment)	Blinding I (performance bias)	Blinding II (detection bias)	Incomplete outcome data (attrition bias)	Reporting bias	Other bias
Dang *et al* (2013)[21]*	Unclear	Low	High	High	Low	Low	Unclear
Oncel *et al* (2014)[22]†	Unclear	Low	High	Low	Low	Low	Low
Percentage of bias across studies							
High	0	0	100%	50%	0	0	0
Low	0	100%	0	50%	100%	100%	50%
Unclear	100%	0	0	0	0	0	50%

*Random sequence generation method not clearly specified. Cards in sealed opaque envelopes were used for allocation concealment to the two study groups. Blinding was not assured for caregivers, parents of treated children, cardiologist evaluating treatment efficacy and researchers evaluating other outcomes. Outcome data were reported for all enrolled neonates. Outcomes of interest included in the study protocol were completely reported. No clear information was provided on concomitant treatment that could affect ductal closure.
†Random sequence generation method not clearly specified. Cards in sequentially numbered sealed opaque envelopes were used for allocation concealment to the two study groups. Blinding was not assured for caregivers, parents of treated children. Blinding was adopted for physician who evaluated the main outcome, but was not assured for researchers evaluating other outcomes. Outcome data were reported for all neonates enrolled. Outcomes of interest included in the study protocol were completely reported. No other source of bias was identified.

There was no significant difference between the paracetamol and ibuprofen groups in terms of mortality, morbidity or ductal reopening (table 4, see online supplementary figures S1–S6).

Evidence from uncontrolled studies

Pooled rate of patients with ductal closure after paracetamol treatment in selected studies, evaluated by proportion meta-analysis, is reported in figures 4 and 5. Subgroup analysis is reported in table 5 (see online supplementary figures S7–S12). A significant improvement in efficacy was observed when paracetamol was used in subjects with GA ≥28 weeks, postnatal age <7 days and when it was used as first-line therapy (table 5; see online supplementary figures S7, S9 and S12). We also observed a trend to greater benefit when paracetamol was used by oral route and at lower dose (table 5, see online supplementary figures S10 and S11). Sensitivity analysis was not applicable considering similar degree of selection bias in the uncontrolled studies. Table 6 shows pooled mortality and morbidity rate, such as pooled rate of ductal reopening for uncontrolled studies enrolling neonates treated with paracetamol calculated by proportion meta-analysis (see online supplementary figures S13–S18).

Safety

Evidence from randomised controlled studies

The safety profile for paracetamol compared with ibuprofen was shown in table 7 (see online supplementary figures S19–S21). Risk of hyperbilirubinaemia was higher for ibuprofen compared with paracetamol (table 7; see online supplementary figure S20).

Evidence from uncontrolled studies

The pooled rate of patients showing side effects and adverse events for uncontrolled studies[7–20] was reported in table 7 (see online supplementary figure S22). A transient increase in aspartate and alanine aminotransferases or γ-glutamyl transpeptidase was reported only in six patients enrolled in three of the 14 uncontrolled studies.[12 16 20]

DISCUSSION

This systematic review meta-analysed, for the first time, RCTs and uncontrolled studies on the use of paracetamol for PDA in the neonate.

There has been increasing interest on the use of paracetamol for the treatment of PDA in the last few years. The first study was published by Hammerman *et al*[7] in 2011 as a case report.

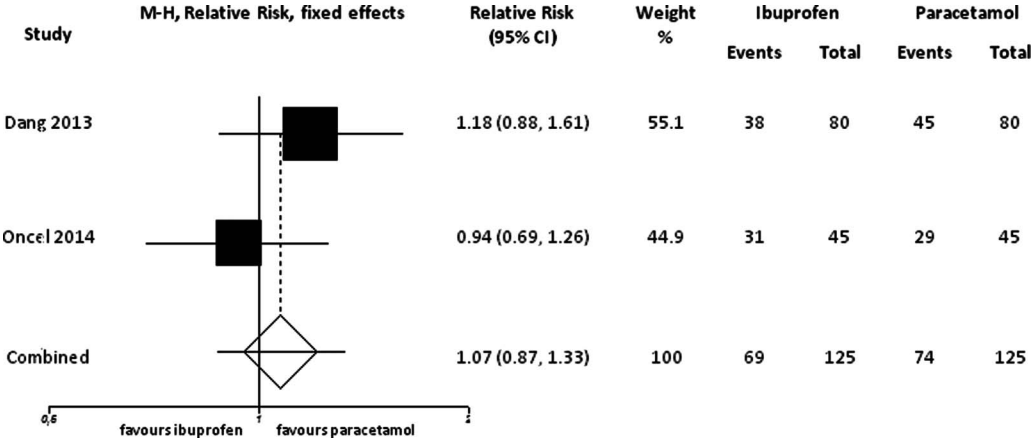

Figure 2 Ductal closure after ibuprofen or paracetamol treatment in randomised controlled trials after 3 days from starting treatment. Cochran Q=1.255; p=0.263; heterogeneity: I^2=0%. Note Analysis performed per intention to treat (Dang *et al*: 8 and 14 subjects withdrawn in the paracetamol and ibuprofen arms, respectively. Oncel *et al*: five and five subjects withdrawn in paracetamol and ibuprofen arms, respectively). M-H, Mantel–Haenszel.

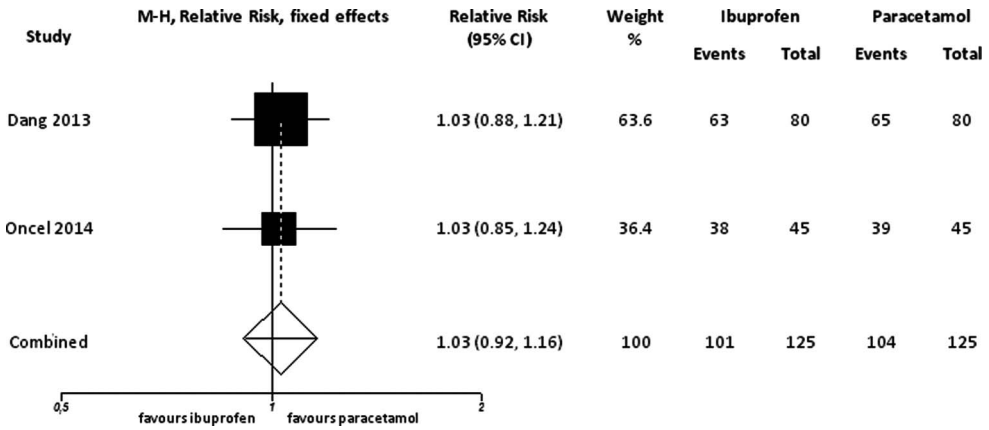

Figure 3 Ductal closure after ibuprofen or paracetamol treatment in randomised controlled trials after 6 days from starting treatment. Cochran Q=0.002; p=0.964; Heterogeneity: I^2=0%. Note. Analysis performed per ITT (Dang *et al*: 8 and 14 subjects withdrawn in paracetamol and ibuprofen arms, respectively. Oncel *et al*: five and five subjects withdrawn in paracetamol and ibuprofen arms, respectively). M-H, Mantel–Haenszel.

Within a few years, another 15 studies were published,[8–22] including, however, only two RCTs.[21 22] In published studies, 246 neonates were treated with paracetamol for PDA (125 patients in RCTs and 121 in uncontrolled studies). Although a limited number of neonates has been studied, in a small number of trials, our results indicate a similar efficacy rate and safety profile of paracetamol and ibuprofen,[3 4] while further RCTs are necessary to explore the relation between clinical features (ie, GA, BW, postnatal age), modalities of administration and the efficacy of paracetamol. To address these aspects, an individual patient meta-analysis would be very valuable. However, analysis of evidence derived from uncontrolled studies[7–20] suggests that efficacy of paracetamol may vary according to some clinical characteristics and modalities of drug administration.

In particular, a reduced efficacy of paracetamol was observed in uncontrolled studies[7–20] for extremely preterm neonates (GA<28 weeks). This phenomenon is not surprising because in more immature neonates, the expression of prostaglandin receptors is greater in the wall of the ductus,[26] and extremely preterm neonates have a thin-walled ductus arteriosus that fails to develop extensive neointimal mounds. Due to these structural limitations in these subjects, functional closure induced by PGHS inhibitors is less frequently followed by the structural closure of the ductus.[27] However, these considerations apply also to COX-i.[28 29]

The analysis of the uncontrolled trials[7–20] also suggests the importance of early treatment of PDA. The greater efficacy of paracetamol observed when treatment was started in the first week of life may depend on the circulating levels of prostaglandins, which are high in the first days of life and decrease as postnatal age increases. This physiological aspect explains, at least in part, the reduced efficacy observed for all PGHS-inhibitory drugs, including ibuprofen and indomethacin, when not administered early in life.[30 31]

Improved efficacy was suggested for paracetamol administered orally compared with the intravenous route when we analysed data derived from uncontrolled studies.[7–20] This difference probably depends on the more steady plasma levels of the drug administered orally, similarly to what observed for the oral use of ibuprofen.[4 32 33] Nevertheless, the higher efficacy rate of the oral route compared with the intravenous route needs to be further explored in specifically designed trials.

The analysis of uncontrolled studies suggests that the use of high doses appears unnecessary. This result should be interpreted with caution considering the high proportion of subjects with GA >28 weeks treated with low doses.[11 20]

By the analysis of the data from uncontrolled studies,[7–20] we observed an impaired efficacy if paracetamol was used after a previous treatment with COX-i, probably because of the delay in administering paracetamol to treat PDA. On the other hand, when paracetamol was administered after COX-i failure, we were unable to rule out that successful closure of ductus may be due to an additive effect of the two drugs rather than paracetamol per se.

Data from both RCTs and uncontrolled trials indicate a good safety profile for paracetamol, at least in the short term. Any

Table 4 Secondary outcomes: meta-analysis of randomised controlled trials

	Number of studies	Paracetamol (n/N)	Ibuprofen (n/N)	Statistical method[24]	RR (95% CI)
Mortality	2[21 22]	18/125	19/125	M-H, fixed*	0.95 (0.52 to 1.72)
Intraventricular haemorrhage	2[21 22]	45/125	49/125	M-H, fixed†	0.92 (0.73 to 1.15)
Necrotising enterocolitis	2[21 22]	6/125	4/125	M-H, fixed‡	1.50 (0.43 to 5.18)
Bronchopulmonary dysplasia	2[21 22]	15/125	21/125	M-H, fixed§	0.71 (0.40 to 1.28)
Retinopathy of prematurity	2[21 22]	13/125	18/125	M-H, fixed¶	0.72 (0.37 to 1.41)
Ductal reopening	2[21 22]	12/104	11/101	M-H, fixed**	1.06 (0.49 to 2.28)

*I^2=0%, p=0.609.
†I^2=0%, p=0.943.
‡I^2=0%, p>0.999.
§I^2=0%, p=0.835.
¶I^2=0%, p=0.821.
**I^2=0%, p=0.507.
M-H, Mantel–Haenszel; n/N, number of events/number of participants; RR, relative risk.

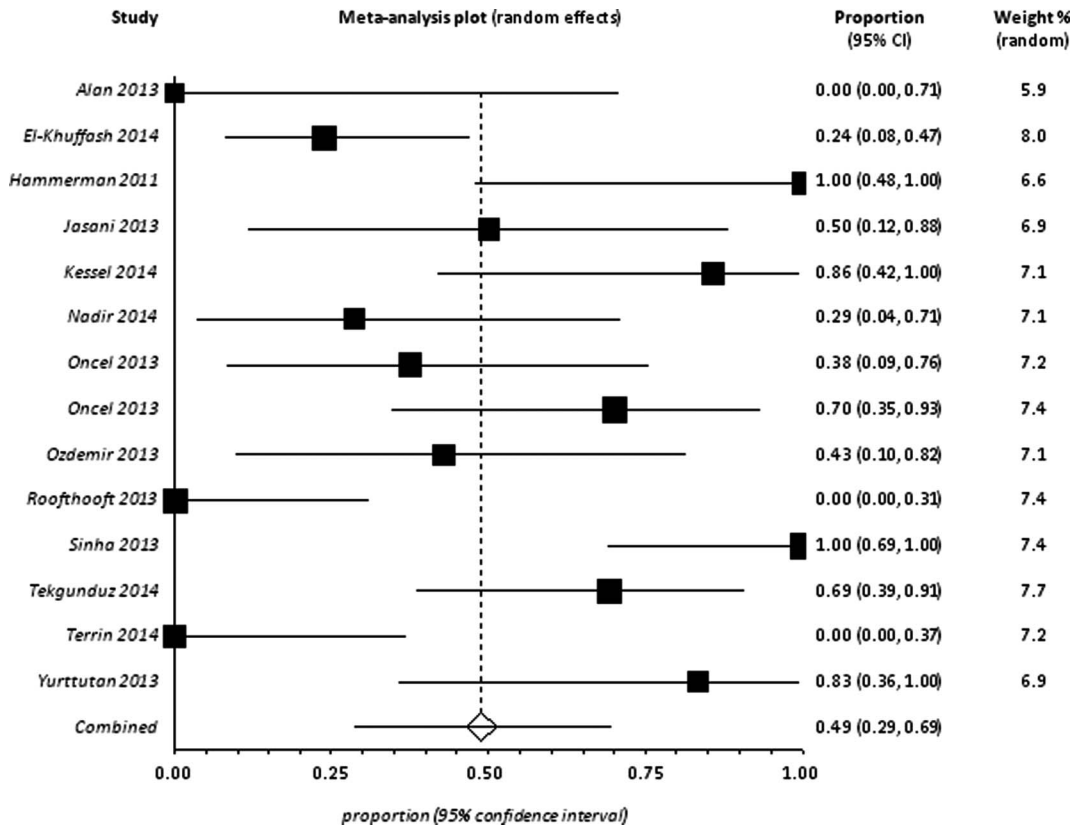

Figure 4 Ductal closure after paracetamol treatment in uncontrolled studies after 3 days from starting treatment. Cochran Q=78.485; p<0.001; heterogeneity: I^2=83%.

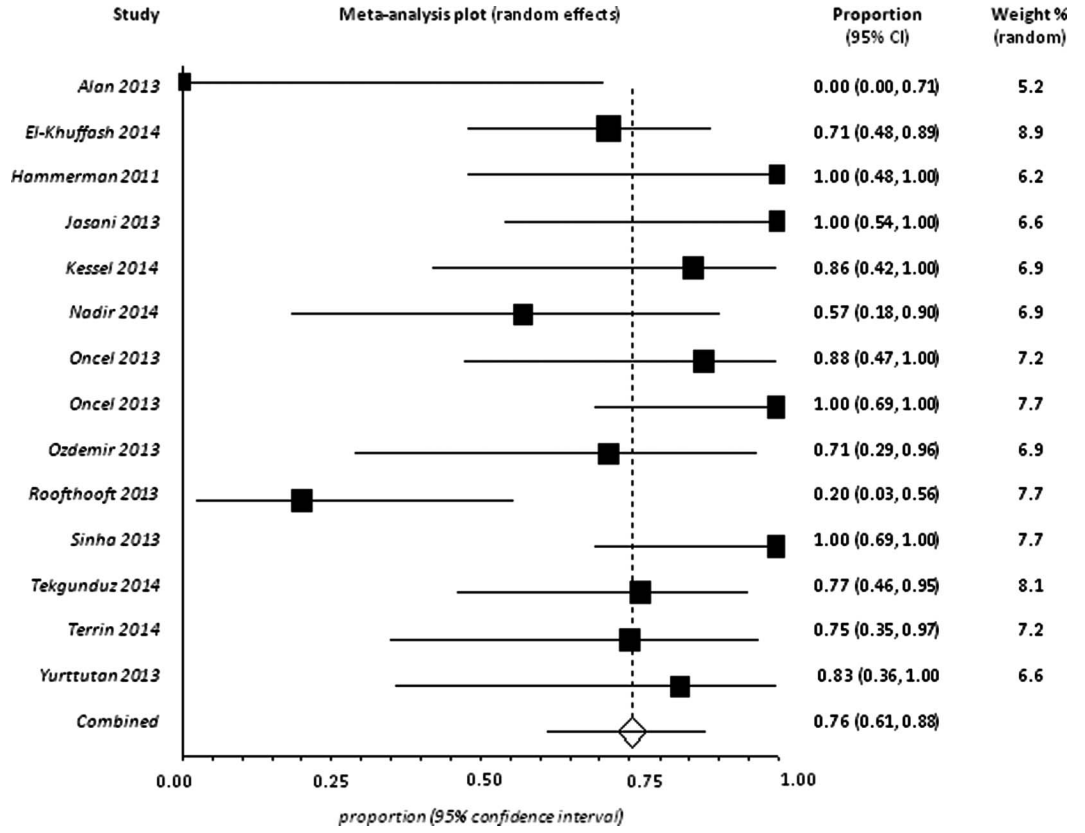

Figure 5 Ductal closure after paracetamol treatment in uncontrolled studies after 6 days from starting treatment. Cochran Q=43.056; p<0.001; heterogeneity: I^2=70%.

Table 5 Pooled ductal closure rate in uncontrolled studies according to clinical characteristics and modalities of paracetamol administration

			Pooled ductal closure at 3 days			Pooled ductal closure at 6 days		
Subgroup	**Number of studies**	**Number of participants**	**Number of responders**	**Proportion, % (95% CI)**	**Statistical method[25]**	**Number of responders**	**Proportion, % (95% CI)**	**Statistical method[25]**
Gestational age								
<28 weeks	13[7–10 12–20]	71	23	39 (20 to 60)	Proportion, random[a]	46	67 (50 to 82)	Proportion, random[b]
≥28 weeks	12[7–12 14–17 19 20]	50	35	66 (44 to 85)*	Proportion, random[c]	46	89 (80 to 96)**	Proportion, fixed[d]
Birth weight								
<1000 g	13[7–14 16–20]	82	35	48 (26 to 70)	Proportion, random[e]	59	74 (57 to 89)	Proportion, random[f]
≥1000 g	10[7 8 10–12 14–16 19 20]	39	23	59 (37 to 79)	Proportion, random[g]	33	82 (70 to 91)	Proportion, fixed[h]
Postnatal age								
≤7 days	11[7–11 15–20]	57	37	65 (41 to 86)	Proportion, random[i]	50	85 (76 to 93)	Proportion, fixed[j]
>7 days	11[7–9 12–16 18–20]	64	21	40 (19 to 62)°	Proportion, random[k]	42	69 (48 to 87)°°	Proportion, random[l]
Route								
Intravenous	6[9 12 13 17 19 20]	52	21	30 (6 to 62)	Proportion, random[m]	38	69 (37 to 94)	Proportion, random[n]
Oral	10[7 8–10 11 14–16 18 19]	69	37	55 (28 to 81)	Proportion, random[o]	54	78 (63 to 90)	Proportion, random[p]
Dose								
High	13[7–10 12–16 18–20]	94	39	42 (23 to 61)	Proportion, random[q]	68	72 (54 to 86)	Proportion, random[r]
Low	3[11 17 20]	27	19	61 (8 to 100)	Proportion, random[s]	24	87 (63 to 99)	Proportion, random[t]
Timing								
First-line therapy	12[7–9 11 13 15–20]	65	40	58 (33 to 81)	Proportion, random[u]	55	83 (74 to 91)	Proportion, fixed[v]
After COX-i failure	10[7 8 12–16 18–20]	56	18	37 (20 to 56)†	Proportion, random[w]	37	66 (41 to 86)‡	Proportion, random[x]

Heterogeneity: (a) I^2=72%, p<0.001. (b) I^2=59%, p=0.004. (c) I^2=65%, p=0.001. (d) I^2=0%, p=0.520. (e) I^2=79%, p<0.001. (f) I^2 68%, p<0.001. (g) I^2=56%, p=0.014. (h) I^2=10%, p=0.350. (i) I^2=75%, p<0.001. (j) I^2=0%, p=0.677. (k) I^2=73%, p<0.001. (l) I^2=69%, p<0.001. (m) I^2=84%, p<0.001. (n) I^2=85%, p<0.001. (o) I^2=84%, p<0.001. (p) I^2=55%, p=0.018. (q) I^2=75%, p<0.001. (r) I^2=71%, p<0.001. (s) I^2=91%, p<0.001. (t) I^2=57%, p=0.098. (u) I^2=80%, p<0.001. (v) I^2=16%, p=0.282. (w) I^2=56%, p=0.015. (x) I^2=74%, p< 0.001.
Subgroup significant χ^2: *p<0.001, **p=0.001; °p<0.001, °°p=0.004; †p=0.001, ‡p=0.017.
COX-i, cyclo-oxygenase inhibitor.

Table 6 Secondary outcomes: meta-analysis of uncontrolled studies

	Number of studies	Number of events	Number of participants	Statistical method[25]	Proportion, % (95% CI)
Mortality	11[8–13 15–18 20]	9	88	Proportion, fixed*	11 (6 to 18)
Intraventricular haemorrhage	11[8–13 15–18 20]	32	88	Proportion, random†	37 (19 to 57)
Necrotising enterocolitis	11[8–13 15–18 20]	4	88	Proportion, fixed‡	6 (2 to 12)
Bronchopulmonary dysplasia	11[8–13 15–18 20]	17	88	Proportion, fixed§	20 (13 to 29)
Retinopathy of prematurity	11[8–13 15–18 20]	11	88	Proportion, fixed¶	14 (8 to 22)
Ductal reopening	13[7–11 13–20]	10	86	Proportion, fixed**	11 (6 to 18)

*I^2=2%, p=0.424.
†I^2=76%, p<0.001.
‡I^2=0%, p=0.788.
§I^2=20%, p=0.248.
¶I^2=0%, p=0.7.
**I^2=21%, p=0.225.

Table 7 Safety profile of pharmacological treatments of patent ductus arteriosus

	Number of studies	Paracetamol (n/N)	Ibuprofen (n/N)	Statistical method[24]	RR (95% CI)
(A) Randomised controlled studies					
Gastrointestinal bleeding	2[21 22]	2/125	9/125	M-H, fixed*	0.26 (0.07 to 1.03)
Hyperbilirubinaemia	1[21]	16/80	28/80	M-H, fixed†	0.57 (0.34 to 0.97)
Oliguria	2[21 22]	6/80	9/80	M-H, fixed‡	0.67 (0.25 to 1.79)
(B) Uncontrolled studies					
	Number of studies	**Paracetamol (n/N)**	**Statistical method[25]**		**Proportion, % (95% CI)**
Increase in liver enzymes	14[7–20]	6/121	Proportion, fixed§		5 (2 to 10)

*I^2=0%, p=0.872.
†I^2=not applicable.
‡I^2=not applicable.
§I^2=29%, p=0.142.
M-H, Mantel–Haenszel; n/N, number of events/number of participants; RR, relative risk.

case of severe adverse events strictly associated with the use of paracetamol was not reported. An increased risk of hyperbilirubinaemia was observed for ibuprofen compared with paracetamol. This effect could be attributable to the ibuprofen albumin binding with consequent bilirubin displacement.[34] A transient increase in aspartate and alanine aminotransferases or γ-glutamyl transpeptidase, without long-term consequences on liver function, has been reported in a small number of neonates receiving paracetamol.[12 16 20] These events were observed only in patients receiving high doses of the drug. Although not statistically significant, a higher number of cases of gastrointestinal bleeding were observed in the ibuprofen group compared with the paracetamol group. This condition may be considered a COX-i-specific side effect, as paracetamol does not induce any damage on the gastrointestinal mucosa.[6] In any case, by the analysis of the available data, it is not possible to establish whether this symptom is related to the drugs or to the other stressful conditions that typically affect premature babies.

The results of this analysis should be interpreted considering the high risk of bias and the limitations of the studies analysed. In particular, the meta-analysis included only two RCTs with a relatively small number of neonates.[21 22] Non-optimal blinding and randomisation methods were adopted in both RCTs. Additionally, two RCTs used paracetamol by the oral route, which is contraindicated in the first days of life in unstable extremely preterm neonates. Most of the studies reviewed, which did not have a comparative arm, showed poor quality and included a small number of patients.[7–20] Finally, the risk that studies showing positive results have a greater likelihood of being published, should also be considered.

In conclusion, a potential role of paracetamol in the management of PDA emerges by this analysis. However, additional well-designed studies are advocated to support the use of paracetamol for PDA in the current clinical practice.

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Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis

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