

The PAIR trial: is paracetamol the way forward in management of hsPDA?

Currently, intravenous (IV) ibuprofen is the only licensed medication for the medical treatment of patent ductus arteriosus (PDA) in the UK; however, there is emerging evidence to suggest that paracetamol may be a promising alternative with fewer side effects. The PAIR pilot trial is the first study in the UK to investigate the efficacy and safety of IV paracetamol in comparison to IV ibuprofen for the management of haemodynamically significant PDA (hsPDA) in preterm infants. This article describes the rationale for the use of paracetamol and the design of the PAIR pilot trial, which will help to inform a much larger future study.

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Background

An IV preparation of ibuprofen is the only licensed medication for the treatment of PDA in the UK; hence, its use as a first line medication to treat hsPDA in preterm babies. It is preferred over other medications, especially indomethacin, because of lesser adverse effects on the gut and kidneys. However, it does come with its own set of side effects.

There is some evidence that while paracetamol confers comparable treatment efficacy to ibuprofen for PDA closure, it has a lower risk of adverse events, particularly relating to acute kidney injury, reduction in gastrointestinal perfusion (risk of necrotising enterocolitis, NEC, or perforation) and/or bleeding. The PAIR trial (Paracetamol And Ibuprofen Research) is the first study in the UK to examine the efficacy and safety of paracetamol in comparison to ibuprofen for treating hsPDA in preterm infants (TABLE 1).

The study objectives

The primary objective of the PAIR trial is to investigate the efficacy of IV paracetamol in treating hsPDA in comparison to IV ibuprofen in preterm infants born at <32 weeks' gestation OR <1,500g birth weight. Infants are treated only if they are ≤28 days of age.

The study design

The trial is currently set up as a single-centre prospective randomised pilot

study conducted at St Mary's Hospital, Manchester. All infants who are clinically symptomatic (requiring any form of respiratory support) and suspected to have a PDA will have an echocardiogram to confirm presence of a hsPDA (defined in TABLE 2). The decision to treat infants with hsPDA will lie with the clinician. If infants are found eligible (TABLE 3) and a decision to treat the hsPDA is made, the parents will be approached. The study will be introduced with a parent information leaflet and once consented, infants will be randomly allocated to receive either IV ibuprofen or IV paracetamol for three days.

Following completion of the course of treatment, an echocardiogram will be repeated within 72 hours to reassess the ductus arteriosus. Conversion of PDA to non-hsPDA (TABLE 2), will be regarded as the trial end point for the primary outcome. If hsPDA persists following completion of the trial medications, participating infants will return to standard care and clinicians will be able to decide on further management of the PDA in keeping with the unit policy (FIGURE 1).

Monitoring during the trial

All infants on trial medications will receive standard care and monitoring. Their vital parameters will be recorded and analysed as per the standard unit policy. Blood tests such as full blood count, renal (urea and electrolytes) and liver function tests (liver enzymes and serum bilirubin), will be

Keywords

patent ductus arteriosus; preterm infants; paracetamol; ibuprofen

Key points

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1. Paracetamol appears to have similar efficacy to ibuprofen in treating hsPDA but with an improved safety profile.
2. The PAIR pilot trial compares paracetamol to ibuprofen in managing hsPDA in infants born at <32 weeks' gestation or birth weight <1,500g.

performed as baseline investigations to ensure suitability and as part of daily monitoring during administration of the trial medications.

Discussion

Association of PDA with adverse neonatal outcomes

Despite several clinical trials over the past decades, management of PDA in premature infants has remained largely unclear. While there are consistent reports of association of PDA with adverse neonatal outcomes (eg chronic lung disease, NEC, acute kidney injury and intraventricular haemorrhage), no clinical trial to date has demonstrated a causal relationship with these negative outcomes. A purist interpretation of such an observation is that PDA is an innocent bystander and better left on its own. On the other hand, there have been several purposeful reviews^{1,2} that have explored the reasons that preclude existing clinical trials from ascribing a causal relationship between ductal patency and adverse outcomes in extreme premature infants. These reviews highlighted issues in the existing trials with:

- selection bias (which results in choosing low risk infants where a PDA is likely to close spontaneously)
- methodological flaws (eg incorrect timing of pharmacological intervention – either too early or too late)
- inappropriate sample size
- contamination of the intervention arm by open label treatments
- use of the same dose of pharmacological treatment across a range of gestations
- bias in the selection of secondary outcomes.

In the last few years, we have witnessed a targeted approach in selecting infants who are likely to be affected by PDA. However, a standardised validated protocol for the diagnosis and treatment of hsPDA remains elusive.^{3,4} There is no uniform consensus on how a hsPDA is defined. Clinical trials continue to utilise a heterogeneous and diverse set of clinical and echocardiographic parameters to reflect the haemodynamic effects of a PDA; hence, it has become difficult to draw meaningful conclusions.

Pharmacological therapies for preterm infants with a PDA

The pivotal roles of prostaglandin and oxygen in mediating ductus arteriosus

Trial title	PAIR (Paracetamol And Ibuprofen Research) pilot trial	
Trial design and clinical phase	Randomised controlled trial, phase II	
Sample size	32 infants	
Planned trial period	Two years	
Investigational medicinal product: dose, route of administration	Group A: ibuprofen IV loading dose at 10mg/kg followed by 5mg/kg IV 24 hourly for two days	Group B: paracetamol IV loading dose at 20mg/kg followed by 10mg/kg/dose every six hours for three days
	Objectives	Outcome measures
Primary outcomes	Efficacy comparison between paracetamol and ibuprofen	Conversion of hsPDA to non-hsPDA
Secondary outcomes	<ol style="list-style-type: none"> 1. Compare BPD-free survival at 36 weeks' PMA 2. Compare the incidence of complications of prematurity in each group 3. To record any evidence of adverse effects with paracetamol or ibuprofen 	<ol style="list-style-type: none"> 1. BPD-free survival at 36 weeks' PMA 2. a) NEC (Bell stage \geqIIa) b) Significant IVH (grade III/IV) c) ROP requiring treatment 3. a) Renal impairment (elevated urea and creatinine > upper limit of normal range) b) Hepatic impairment (elevated liver enzymes ALT or AST > upper limit of normal) c) Significant gastrointestinal or non-gastrointestinal bleeding requiring intervention

TABLE 1 The PAIR trial summary. Key: PDA=patent ductus arteriosus; hsPDA=haemodynamically significant PDA; PMA=post menstrual age; BPD=bronchopulmonary dysplasia; NEC=necrotising enterocolitis; IVH=intraventricular haemorrhage; ROP=retinopathy of prematurity; ALT=alanine aminotransferase; AST=aspartate transaminase.

hsPDA: any three of the following six criteria	Non-hsPDA: PDA closed or any two of the following three parameters
PDA diameter \geq 2.0mm in 2D image	Reduction of PDA diameter >50% (2D image)
Ductal flow pattern ('growing' pattern or pulsatile with Vmax/Vmin \geq 2)	Restrictive or closing ductal flow pattern
Retrograde diastolic flow in post-ductal aorta, coeliac artery, SMA	LA:Ao ratio <1.5
LA:Ao ratio \geq 2	
LVO \geq 300mL/kg/min	
Mitral valve E/A ratio \geq 1	

TABLE 2 Echocardiographic criteria for hsPDA/non-hsPDA. Key: LA:Ao=left atrial to aortic root ratio; LVO=left ventricular output; SMA=superior mesenteric artery; E/A=E wave to A wave ratio.

closure were uncovered back in the 1970s, which led to the introduction of pharmacological therapies for preterm infants with a PDA.⁵ Cyclooxygenase (COX) inhibitors block prostaglandin synthesis and are effective in ductal closure. Among the non-selective COX inhibitors, indomethacin was the first drug used for PDA treatment, presenting a closure rate of about 75-80%.⁶ It was widely used as first line standard therapy for several years; however, its use was marred by several unacceptable side effects primarily resulting from high

vasoconstrictor action. Impairment in renal function (acute renal failure and chronic renal failure), oliguria, proteinuria, hyperkalaemia, cerebral white matter damage, NEC, intestinal perforation (especially when co-administered with corticosteroids) and platelet dysfunction were noted.⁷

Ibuprofen, another non-selective COX inhibitor, shares the same mechanism of action in effecting ductal closure as indomethacin, but it has lower vasoconstrictor side effects. Ibuprofen,

therefore, has a relatively lesser impact on the microcirculation and consequent impairment of renal function. This difference may be partly explained by a preferential effect of indomethacin on COX-1 instead of COX-2 receptors, but there are other mechanisms that not fully understood.⁷

A recent systematic review compared ibuprofen with indomethacin in the treatment of hsPDA.⁸ It summarised findings from 39 randomised and quasi-randomised trials, which had enrolled a total of 2,843 infants. The review concluded that ibuprofen was not only as effective as indomethacin in closing a PDA, but also caused fewer side effects on the kidneys and reduced the risk of NEC. Now, ibuprofen has largely replaced indomethacin in most of the world and remains the only licensed medication for treatment of PDA in preterm infants in the UK.⁹ That said, although ibuprofen appears to be ‘friendlier’ than indomethacin, it is still far from ideal and is not without its own side effects; the hunt for a safer pharmacological agent continues.

Is paracetamol the way forward?

Vasoconstriction is generally believed to be the primary causative factor for renal impairment, cerebral ischaemia and NEC and these side effects are common with the use of non-steroidal anti-inflammatory

drugs (NSAIDs), such as ibuprofen and indomethacin. Since the first case report by Hammerman et al in 2011,¹⁰ several observational studies have indicated paracetamol as a safer alternative medication to ibuprofen.

Paracetamol’s advantage over conventional NSAIDs can be related to its unique mechanism of action. Paracetamol is not a classic NSAID, having only weak anti-platelet and anti-inflammatory activity; it exerts mainly central effects (as an analgesic and antipyretic). It reduces the synthesis of prostaglandins through the inhibition of prostaglandin synthetase, as happens with NSAIDs, but acts at a different enzyme site, called the peroxidase region. More interestingly, paracetamol exerts a vasodilatory effect,¹¹ which may explain the fewer adverse effects encountered with paracetamol use in clinical practice.

A recent national survey¹² in the UK has highlighted that 82% (49 of 60) of neonatal intensive care units (NICUs) use paracetamol for management of hsPDA. It was observed that, while the majority of NICUs (65%) used it as a second-line treatment for PDA, 10% use it as a first-line treatment in preference to ibuprofen. While paracetamol has shown a lot of promise, definitive evidence to support its use in this vulnerable population is not yet established.

A systematic review¹³ of paracetamol recognised it as a promising alternative to ibuprofen with a better safety profile but was unable to provide practice recommendations due to the heterogeneity in the methodology and designs of the available clinical trials. Assurance regarding its optimum dosage, route of administration, short and long-term implications from studies conducted so far remains limited.

We have reviewed all of the existing randomised controlled trials (RCTs) involving the use of IV paracetamol (TABLE 4). To date, only three RCTs were noted to compare IV paracetamol directly with IV ibuprofen. These were all single-centre trials. While Mashad et al¹⁴ observed similar efficacy of paracetamol in comparison to ibuprofen and indomethacin, Tauber et al¹⁵ reported no effect with a first course of ibuprofen whereas Dani et al¹⁶ noticed paracetamol to be much less effective in comparison to ibuprofen in ductal closure.

Inclusion criteria	Exclusion criteria
1. Gestational age <32 weeks	1. Contraindication for administration of ibuprofen or paracetamol such as: <ul style="list-style-type: none"> • active bleeding (eg intracranial or gastrointestinal haemorrhage) • thrombocytopenia (<50x10⁹/L) • renal failure (raised creatinine >100µmol/L, or oliguria <0.5mL/kg/hour) • confirmed or suspected NEC (modified Bell staging ≥IIa) • any gastric or intestinal perforation
2. Birth weight <1,500g	2. Pre-treatment abnormal liver function tests (ALT > upper normal limit of the reference range; pre-treatment bilirubin > NICE exchange phototherapy level)
3. Postnatal age ≤28 days	3. Previous use of ibuprofen or paracetamol prior to randomisation
4. Meets criteria for hsPDA	4. Persistent pulmonary hypertension (ductal right-to-left shunt ≥33% of cardiac cycle)
5. Clinician’s decision to treat PDA	5. Congenital heart defect other than PDA or PFO
	6. Life-threatening congenital birth defects
	7. Chromosomal abnormalities and/or congenital anomalies associated with abnormal neurodevelopment

TABLE 3 The PAIR trial: inclusion and exclusion criteria. Key: NICE=National Institute for Health and Care Excellence; PFO=patent foramen ovale.

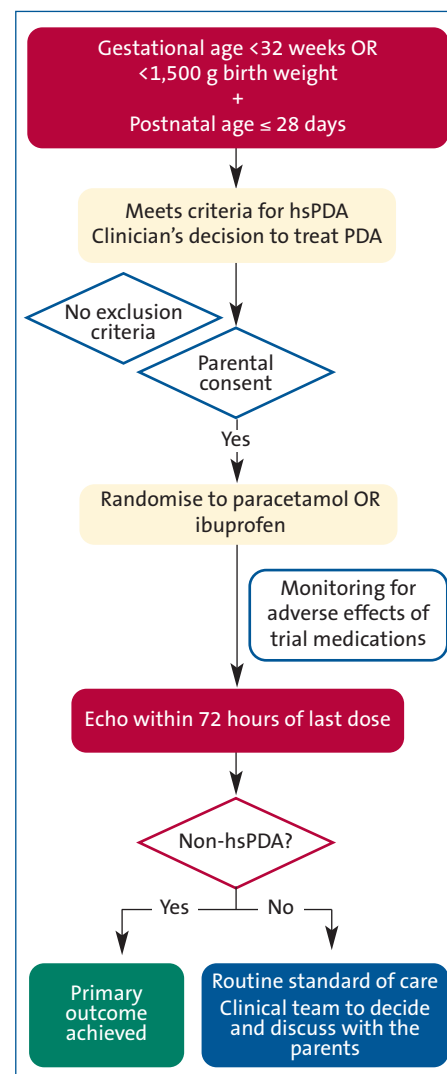


FIGURE 1 The PAIR protocol flowchart.

Authors	Year/country/ intervention	Sample size	Eligible population (gestation)	Regime	Total cumulative dose (mg/kg)	Therapeutic efficacy and statistical significance	Side effects of PCM
Harkin et al ¹⁷	2016 Finland PCM (n=23) Placebo (n=25)	48	<32 weeks	20mg/kg loading dose followed by 7.5mg/kg every 6h for 4 days	132.5	Early closure of PDA (177 hours vs 338 hours). Significant against placebo	No detectable adverse effects
El-Mashad et al ¹⁴	2017 Egypt PCM (n=100) Ibuprofen (n=100) Indomethacin (n=100)	300	<28 weeks/ <1,500g	15mg/kg every 6h for 3 days	180	80% PCM group vs 77% ibuprofen vs 81% indomethacin. Second treatment course: 88% PCM vs 83% ibuprofen vs 87% indomethacin. Not significant	PCM has fewer side effects mainly on renal function, platelet count and GI bleeding. Significant increase in creatinine and BUN in ibuprofen and indomethacin group along with oliguria and thrombocytopenia
Bagheri et al ²³	2018 Iran PCM (n=80) Placebo (n=80)	160	≤34 weeks	20mg/kg loading dose followed by 7.5mg/kg every 6h for 3 days	102.5	PDA in PCM group = 15% vs 71.25% in placebo group. Statistically significant	No hepatic complications occurred during hospital stay
Hochwald et al ¹⁸	2018 Israel PCM + ibuprofen (n=12) Placebo + ibuprofen (n=12)	24	<32 weeks	20mg/kg loading dose followed by 10mg/kg every 6h for 3 days (total = 12 doses)	130	83% PCM vs 42% placebo. Not significant (p<0.08)	No adverse effects clinical or laboratory noted in PCM group
Dani et al ¹⁶	2020 Italy PCM (n=58) Ibuprofen (n=52)	110	<32 weeks	15mg/kg every 6h for 3 days	180	PCM 52% closure rate vs ibuprofen 78%. Success rates in constriction were similar. Not significant	No difference in adverse effects between the two groups
Meena et al ²⁴	2020 India PCM (n=35) Oral ibuprofen (n=35) Oral indomethacin (n=35)	105	<37 weeks	15mg/kg every 6h for 3 days	180	Cumulative closure rate 71.43% PCM group vs 77.14% ibuprofen vs 68% indomethacin. Not significant	IV paracetamol has better safety profile; serum creatinine and BUN significantly raised in the indomethacin and ibuprofen groups
Tauber et al ¹⁵	2020 USA PCM (n=5) IV ibuprofen (n=5)	10	<30 weeks	15mg/kg every 6h for 3 days	180	40% in PCM group vs 100% in ibuprofen group needed subsequent pharmacological treatment	No side effects in either group
Schindler et al ²⁵	2021 Australia PCM (n=29) Placebo (n=29)	58	<29 weeks	15mg/kg loading dose followed by 7.5mg/kg every 6h for 5 days	157.5	Infants in PCM group required PDA intervention 21% vs placebo group 59%. PDA closure in PCM group 69% vs placebo group 28%. Statistically significant	No adverse effects reported in PCM group
Davidson et al ²⁶	2021 USA PCM (n=17) Indomethacin (n=20)	37	≤32 weeks or ≤1,500g	15mg/kg every 6h for 3 days	180	One (5.9%) hsPDA in the PCM group had successful treatment compared to 11 (55%) in the indomethacin group	The side effects with both drugs were similar

TABLE 4 Summary of RCTs using IV paracetamol for PDA management. Key: PCM=paracetamol; GI=gastrointestinal; BUN=blood urea nitrogen; echo=echocardiography.

Paracetamol administration in the PAIR trial

The dosage, duration, and the route of paracetamol administration in the PAIR trial has been carefully extrapolated from the available evidence in the literature. Although a number of these trials have used higher cumulative doses of paracetamol (ranging up to 180mg/kg for a course), lower cumulative doses of as low as 102.5mg/kg to 130mg/kg have been shown to be equally effective.¹⁷⁻¹⁹ In addition, cumulative doses of 180mg/kg have been associated with hepatic toxicity.²⁰ Terrin et al²⁰ recommended a limitation of dosing to 45mg/kg/day to avoid potential toxicity and still demonstrated similar efficacy rates to those of higher doses. From these, as well as from the pharmacokinetic study performed by Allegaert et al,⁶ the paracetamol treatment regime of loading dose of 20mg/kg followed by 10mg/kg every six hours for three days was chosen for the PAIR trial. This regimen promises a consistent steady state level of paracetamol and uses a relatively lower cumulative dose (130mg/kg) for the entire course.

One of the biggest advantages of the chosen paracetamol regimen in the PAIR trial is that, while it confers similar efficacy (up to 80% for closing ductal patency), in comparison to the higher cumulative doses used in other trials, there are no reported side effects in the literature. The current evidence regarding the pharmacokinetic and pharmacodynamic properties of paracetamol for hsPDA closure in extreme preterm infants can be seen in our recent article in a previous issue of *Infant*.²¹

Echocardiography in the PAIR trial

In the UK, echocardiograms are mostly performed by neonatologists. The echocardiogram indices for hsPDA have been extrapolated from the widely accepted recommendations by the European Special Interest Group on Neonatologist Performed Echocardiography.²² While the jury is still out on the evidence-base of echocardiogram parameters for diagnosis of hsPDA, both the treatment groups in the PAIR trial are diagnosed using the same echocardiogram parameters, therefore the echocardiography is unlikely to introduce bias or interfere with the objective of the trial. The PAIR trial defines non-hsPDA as a state in which the PDA is either closed or is insignificant and therefore unable to affect the infant adversely.

PAIR: the way forward

Many neonatologists remain in equipoise on the perils of a PDA versus the safety of administering a pharmacological treatment. Nevertheless, neonatologists continue to use pharmacological treatments to manage a PDA. We envisage that paracetamol has the potential to provide a credible alternative to ibuprofen as the drug of choice.

Although the PAIR trial is a single-centre, open label pilot study, going forward the results of this pilot study will answer questions on the efficacy and long-term safety of paracetamol in management of hsPDA through a large-scale, double blinded, randomised controlled, non-inferiority multicentre phase III/IV PAIR trial. Such a trial will also aim to gather information on long-term neurodevelopmental outcomes between 18-24 months corrected gestational age through follow-up data and PARCA-R questionnaire (Parent Report of Children's Abilities – Revised). Paracetamol is a much cheaper drug than ibuprofen and, hence, a pharmaco-economic analysis as part of this multicentre trial will enable us to assess cost effectiveness.

Trial progress and contact information

The PAIR trial is currently running as a single-centre randomised pilot trial. Approval from regulatory bodies such as the Research Ethics Committee, the Medicines and Healthcare products Regulatory Agency (MHRA) and the Integrated Research Application System (IRAS; ID 100053) have been obtained. The study is sponsored by Manchester University NHS Foundation Trust and is registered in the clinicaltrials.gov website (ClinicalTrials.gov identifier= NCT04986839). The trial duration is two years and the sample size for this pilot trial is 32 infants, which has been estimated from a local audit. The full trial protocol, study information leaflets and further information can be requested by contacting pairtrial@gmail.com or Twitter @PairTrial.

References

1. **Smith A, El-Khuffash A.** Patent ductus arteriosus clinical trials: lessons learned and future directions. *Children (Basel)* 2021;8:47.
2. **Evans N.** Preterm patent ductus arteriosus: a continuing conundrum for the neonatologist? *Semin Fetal Neonatal Med* 2015;20:272-77.

3. **Smith A, El-Khuffash AF.** Defining 'haemodynamic significance' of the patent ductus arteriosus: do we have all the answers? *Neonatology* 2020;117: 225-232.
4. **Hamrick SEG, Sallmon H, Rose AT, et al.** Patent ductus arteriosus of the preterm infant. *Pediatrics* 2020;146:e20201209
5. **Obladen M.** History of the ductus arteriosus: 1. Anatomy and spontaneous closure. *Neonatology* 2011;99:83-89.
6. **Allegaert K, Anderson B, Simons S, van Overmeire B.** Paracetamol to induce ductus arteriosus closure: is it valid? *Arch Dis Child* 2013;98:462-66.
7. **Bardanzellu F, Neroni P, Dessi A, Fanos V.** Paracetamol in patent ductus arteriosus treatment: efficacious and safe? *Biomed Res Int* 2017; 2017:1438038.
8. **Ohlsson A, Walia R, Shah SS.** Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database of Syst Rev* 2018;9:CD003481.
9. **British National Formulary for Children.** Online at: <https://bnfc.nice.org.uk/treatment-summary/drugs-affecting-the-ductus-arteriosus.html>
10. **Hammerman C, Bin-Nun A, Markovitch E, et al.** Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. *Pediatrics* 2011;128(6):e1618-21.
11. **van der Horst J, Manville RW, Hayes K, et al.** Acetaminophen (paracetamol) metabolites induce vasodilation and hypotension by activating Kv7 potassium channels directly and indirectly. *Arterioscler Thromb Vasc Biol* 2020;40:1207-19.
12. **Mukherjee A, Jadhav V, Gupta A.** Off-label use of paracetamol in managing patent ductus arteriosus across neonatal intensive care units in the UK. *Arch Dis Child Fetal Neonatal Ed* 2021;106:113-14.
13. **Xiao Y, Liu H, Hu R, You Q, et al.** Efficacy and safety of paracetamol for patent ductus arteriosus closure in preterm infants: an updated systematic review and meta-analysis. *Front Pediatr* 2019;7:568.
14. **El-Mashad AE-R, El-Mahdy H, El Amrousy D, Elgendy M.** Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. *Eur J Pediatr* 2017;176:233-40.
15. **Tauber KA, King R, Colon M.** Intravenous acetaminophen vs intravenous ibuprofen to close a patent ductus arteriosus closure: a pilot randomized controlled trial. *Health Sci Rep* 2020;3:e183.
16. **Dani C, Poggi C, Cianchi I, et al.** Effect on cerebral oxygenation of paracetamol for patent ductus arteriosus in preterm infants. *Eur J Pediatr* 2018;177:533-39.
17. **Harkin P, Harma A, Aikio O, et al.** Paracetamol accelerates closure of the ductus arteriosus after premature birth: a randomized trial. *J Pediatr* 2016;177:72-77.e2.
18. **Hochwald O, Mainzer G, Borenstein-Levin L, et al.** Adding paracetamol to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: a double-blind, randomized, placebo-controlled pilot study. *Am J Perinatol* 2018;35:1319-25.
19. **Tekgunduz KS, Ceviz N, Caner I, et al.** Intravenous paracetamol with a lower dose is also effective for the treatment of patent ductus arteriosus in preterm infants. *Cardiol Young* 2015;25:1060-64.
20. **Terrin G, Conte F, Scipione A, et al.** Efficacy of paracetamol for the treatment of patent

- ductus arteriosus in preterm neonates. *Ital J Pediatr* 2014;40:21.
21. **Gupta A, Mukherjee A.** Do we know how to treat PDA with paracetamol? Current evidence on the pharmacokinetics and pharmacodynamics of paracetamol for hsPDA closure in extreme preterm infants. *Infant* 2021; 17(5):186-93.
22. **Groves AM, Singh Y, Dempsey E, et al.** European Special Interest Group Neonatologist Performed Echocardiography (NPE). Introduction to neonatologist-performed echocardiography. *Pediatr Res* 2018;84(suppl 1):1-12.
23. **Bagheri MM, Bahman-Bijari B, Torabi-Nejad MH, et al.** Is prophylactic parenteral paracetamol effective to diminish incidence of PDA in preterm neonates? A randomized trial. *Iran J Pediatr* 2018;28:e11735.
24. **Meena V, Meena DS, Rathore PS, et al.** Comparison of the efficacy and safety of indomethacin, ibuprofen, and paracetamol in the closure of patent ductus arteriosus in preterm neonates – a randomized controlled trial. *Ann Pediatr Cardiol* 2020;13:130-35.
25. **Schindler T, Smyth J, Bolisetty S, et al.** Early PARacetamol (EPAR) trial: a randomized controlled trial of early paracetamol to promote closure of the ductus arteriosus in preterm infants. *Neonatology* 2021;118:274-81.
26. **Davidson JM, Ferguson J, Ivey E, et al.** A randomized trial of intravenous acetaminophen versus indomethacin for treatment of hemodynamically significant PDAs in VLBW infants. *J Perinatol* 2021;41:93-99.

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