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**Oral medications regarding their safety and efficacy in the management of patent ductus arteriosus**

Oncel MY *et al.* Oral medications in the management of PDA

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**Abstract**

Patent ductus arteriosus (PDA) is a common clinical condition in preterm infants which is inversely related to birth weight and gestational age. Cyclooxygenase inhibitors such as indomethacin and ibuprofen which block the prostaglandin conversion from arachidonic acid are the most commonly used drugs for ductal closure. This review focuses on the safety and efficacy oral medications in the management of PDA in preterm infants. Ibuprofen seems to be the first choice due to its higher safety profile, as it is associated with fewer gastrointestinal and renal side effects when compared to indomethacin. PDA closure rates are better with oral than with intravenous ibuprofen probably due to the pharmacokinetic of the drug. However, these medications were reported to be associated with several adverse including transient renal failure, gastrointestinal bleeding and perforation, hyperbilirubinemia and platelet dysfunction. Paracetamol seems be an alternative to PDA therapy with lower adverse events and side effects.

**Key words:** Efficacy; Ibuprofen; Oral; Paracetamol; Patent ductus arteriosus; Preterm infant; Safety

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**Core tip:** Regarding to the management of patent ductus arteriosus (PDA) in preterm infants, neonatologists and cardiologists have not reached a consensus on which PDAs to treat, when to treat, and how to treat. Currently, ibuprofen seems to be the first choice due to its higher safety profile, as it is associated with fewer gastrointestinal and renal side effects when compared to indomethacin. PDA closure rates are better with oral than with intravenous ibuprofen. Recent studies suggest that paracetamol can be a medical alternative in the management of PDA with similar efficacy but lower side events than nonsteroidal anti-inflammatory drugs.

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**INTRODUCTION**

Patent ductus arteriosus (PDA), of which incidence is inversely related to gestational age (GA), is the most common cardiac condition among preterm infants. It is estimated to be 55% in preterm infants born before 28 wk’ GA and weighing < 1000 g[1,2]. Several comorbidities are associated with a PDA, but whether PDA is responsible for their development or not is still unclear[3,4].

The treatment options for PDA closure are pharmacological and surgical. Prostaglandin-H2 synthetase (PGHS) enzyme system, which has two active sites as cyclo-oxygenase (COX) and peroxidase (POX), produces circulating prostaglandins (PGs) that regulate ductal patency[5,6]. Nonsteroidal anti-inflammatory drugs (NSAIDs), especially indomethacin and ibuprofen, are widely used for management of hemodynamically significant (hs)-PDA[7,8]. Ductal closure rate of PDA’s pharmacological treatment is among 70%-85%[9-11]. COX-1 is constitutively expressed in different tissues, all NSAIDs can determine many side effects, mainly in cerebral, gastrointestinal and renal districts. In addition, there are some known contraindications such as renal failure, thrombocytopenia, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and severe hyperbilirubinemia for ibuprofen or indomethacin administration. Therefore, there is a burden for alternative therapies which may result in at least equal closure rates but with fewer side effects[12-14].

Paracetamol (acetaminophen), unlike ibuprofen, directly inhibits the activity of prostaglandin synthase by acting at the POX region of the enzyme. Paracetamol inhibition is facilitated by a decreased local concentration of hydroperoxides[15,16]. The role of paracetamol as an alternative therapy for hs-PDA closure has gained attention in recent years because of the potential adverse effects of COX inhibitors[17-19]. In our previously reported case series, we showed that intravenous (IV) paracetamol could be an alternative treatment in patients in whom feeding was contraindicated or who had feeding intolerance[19]. Our recent studies show that paracetamol in oral form can be used successfully as the primary choice in PDA closure[20,21].

The main point of this review is the safety and efficacy oral medications in management of PDA in preterm infants. One commonly used therapeutic (oral ibuprofen) and a new alternative medication as oral paracetamol are discussed.

**ORAL IBUPROFEN**

Ibuprofen currently appears to be the drug of choice depending on its similar efficacy but lower side effect profile in comparison to indomethacin in closing PDA. It is effective in closing PDA without reducing renal, cerebral or intestinal blood flow[22-24]. The rate of PDA closure in preterm infants varies both due to the dose regimens and the repeated courses of ibuprofen. The recommended dose regimen is 10 mg/kg loading dose followed by 5 mg/kg per day every 24 h for next two days[25,26]. A higher dose regimen as 20-10-10 mg/kg can result in a higher closure rate especially in lack of response to ordinary regimen, but must be balanced with side effect profile of the drug[26]. Individualizing the treatment by dosing COX inhibitors based on plasma concentrations has been discussed in the literature. The serum concentration after the first dose of ibuprofen was reported as the most important factor for a successful ductal closure[27].

Ibuprofen prophylaxis is also reported in various studies. Recently, Cochrane update[28] evaluated seven studies comparing prophylactic ibuprofen with placebo/no intervention. According to their results ibuprofen decreases the incidence of PDA on day three, the need for PDA treatment with NSAIDs and surgical ligation. In aspect of side effects, ibuprofen prophylaxis negatively affects renal function, increases risk of gastrointestinal bleeding but has no significant differences in mortality, IVH and bronchopulmonary dysplasia (BPD). In conclusion, this meta-analysis included two prophylaxis studies with oral ibuprofen and concludes that until long-term follow up results of these studies are published, no further trials of prophylactic ibuprofen are recommended. Similarly, we had terminated our recent study with oral ibuprofen prophylaxis according to observed serious side effects such as gastrointestinal bleeding, isolated intestinal perforation and renal failure in first days of life[29].

Aly *et al*[30] compared intravenous indomethacin and oral ibuprofen and the results of the study showed that oral ibuprofen is as effective as intravenous indomethacin. Because of preference of ibuprofen in contrast to indomethacin, new researches have focused on oral ibuprofen. A prospective- randomized study by Cherif *et al*[31] showed that ductal closure rate with oral ibuprofen was at least as effective as the intravenous route (84.3% *vs* 62.5%, *P* = 0.04) and oral ibuprofen was associated with fewer side effects. Our randomized controlled trial (RCT) demonstrated that oral ibuprofen was more successful than IV ibuprofen (84.6% *vs* 62%) in the management of PDA in very low birth weight (VLBW) infants. A higher increase in cystatin-C level, a marker of impaired renal function, with oral ibuprofen than intravenous form indicated that infants with borderline renal function should be carefully monitored[10]. In a similar designed study now in extremely low birth weight preterm infants, we demonstrated a similar initial closure rate but a higher reopening rate in infants who received ibuprofen when compared to our previous study in VLBW preterm infants[10,11]. A meta-analysis including three trials comparing oral with IV ibuprofen (*n* = 236) showed a significantly lower failure rate of PDA closure in favor of oral ibuprofen (RR = 0.42; 95%CI: 0.26-0.67); (RR = -0.22; 95%CI: -0.35 to -0.11); NNT 5 (95%CI: 3-9) with similar rates of side effects[32]. Recent Cochrane review in 2015 concluded that oral ibuprofen was associated with a decreased risk of failure to close a PDA in comparison to IV ibuprofen[33].

Oral ibuprofen is associated with GI bleeding, NEC and spontaneous intestinal perforation (SIP)[34-36]. However, SIP was reported in both arms of intravenous and oral administration of the drug in RCTs comparing oral and intravenous ibuprofen or intravenous ibuprofen and indomethacin for PDA treatment. Additionally, the meta-analysis by Ohlsson failed to detect a statistically significant difference between oral ibuprofen and intravenous ibuprofen for all the gastrointestinal complications associated with administration of NSAIDs (GI bleeding, NEC and SIP)[37]. We suggest to use oral ibuprofen after oro-gastric feeding and flush it with 1-2 mL of distilled water to decrease its osmolarity related side effects on GIS.

Ibuprofen can compete with bilirubin for albumin binding sides and may induce bilirubin encephalopathy[38,39]. There is no definitive opinion on the effect of ibuprofen on bilirubin. In vitro studies suggest that ibuprofen may displace bilirubin from albumin binding sites, since it is 99% protein bound, increasing the risk of kernicterus[38]. Zecca *et al*[40] discussed the role of competition between ibuprofen and bilirubin and showed that ibuprofen use was associated with increase in total serum bilirubin levels and longer phototherapy duration.

Persistent pulmonary hypertension of the newborn (PPHN) was also observed, soon after the administration of IV ibuprofen, in the context of a randomized prophylactic trial, which was prematurely discontinued before full enrolment due to the development of this adverse effect[41]. After administration of oral ibuprofen, PPHN has not been observed in any study. Gournay *et al*[41] alerted physicians about the possibility of PPHN after the loading dose of ibuprofen, and hypothesized that PPHN could be related either to the early drug administration or to a drug-induced pulmonary microembolism.

In conclusion, ibuprofen is contraindicated in treatment of PDA in preterm infants with PDA-dependent congenital heart disease, renal failure, severe hyperbilirubinaemia, sepsis, NEC, gastrointestinal perforation, active bleeding from any site, severe thrombocytopenia and hypersensitivity to ibuprofen[42].

***Oral paracetamol: a new approach to PDA treatment***

Paracetamol is emerging as a possible alternative to indomethacin and ibuprofen following a chance observation made by Hammerman *et al*[17] in a baby with PDA who was given paracetamol for pain relief. The effect of paracetamol is at the peroxidase segment of prostaglandin synthase[43].

There has been increasing interest on the use of paracetamol for the treatment of PDA in the last few years. In the first case series by Hammerman *et al*[17] oral paracetamol (15 mg/kg per dose/6 h for 3 d) was effective in five patients who did not respond to ibuprofen. In our previous case series with a median GA of 28.5 wk and a median birthweight of 995 g, paracetamol was administered after a median of 9.5 d (5-27) from birth in 8 preterm infants who did not respond to 2 sequential courses of ibuprofen and/or for whom treatment with ibuprofen was contraindicated[18]. The hs-PDA closed in 7 of the infants[18]. In our other case series, we used intravenous paracetamol in 10 preterm infants with hs-PDA in whom feeding was either not tolerated or contraindicated, and the PDA closure was successful in all patients[19]. In a case series by Yurttutan *et al*[20] that was conducted to investigate the efficacy of paracetamol as the first choice for the treatment of PDA in 6 preterm infants, 5 infants were successfully treated.

Our recent prospective RCT demonstrated that the PDA closure rate was similar for ibuprofen (77.5%) and paracetamol (72.5%) after the first course of the treatment[21]. In addition, both oral medications were well-tolerated and deemed safe in terms of renal and liver variables, as well as a lack of statistically significant difference in major complications (renal tolerance, hypertransaminasemia, hyperbilirubinemia, gastrointestinal bleeding, NEC, IVH, BPD, and ROP). Similarly, Dang *et al*[44] randomized 160 babies born before 34 wk to oral ibuprofen versus oral paracetamol in a non-blinded trial. Overall closure rates were similar at 79% versus 81% respectively with less gastrointestinal bleeding and less jaundice in the paracetamol group. There was not any significant differences in other side effects.

In particular, a reduced efficacy of paracetamol was observed in uncontrolled studies for extremely preterm neonates (GA < 28 wks)[45]. This phenomenon is not surprising because in more immature neonates, the expression of prostaglandin receptors is greater in the wall of the ductus, 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[5,46].

IV paracetamol may transiently increase liver enzymes concentration in patients[47]. Alan *et al*[48] reported 3 patients with transient increased transaminases, which they observed with IV paracetamol use. Moreover, serious acute liver toxicity events have been reported in neonates when using intravenous formulation of paracetamol[49-52]. The slow oxidative metabolism of neonates, production of toxic metabolites in their livers, and increased rate of glutathione synthesis are mechanisms that may confer protection in the context of an overdose[52-54]. N-acetylcysteine, which detoxifies the toxic metabolite N-acetyl-p-benzoquinone imine, appears to be safe in the neonate but there is no data on its use in patients treated for PDA[52,55].

Measurement of serum paracetamol concentration was performed in only two studies with PDA management. In particular, Oncel *et al*[19] measured serum levels of paracetamol on days 1 (7.3 mcg/mL), 2 (15.5 mcg/mL) and 3 (14.7 mcg/mL) of treatment; while in the study by Yurttutan *et al*[20] evaluated serum paracetamol only after 24 h from the first dose and values ranged from 5 to 18 mcg/mL. All these values were within the therapeutic range for children (10-30 mcg/mL)[56].

Terrin *et al*[45] evaluated 2 RCTs and 14 uncontrolled studies on paracetamol use for the management of PDA. This meta-analysis of RCTs does not demonstrate any difference in the risk of ductal closure. Proportion meta-analysis of uncontrolled studies demonstrates a pooled ductal closure rate of 49% (95%CI: 29%-69%) and 76% (95%CI: 61%-88%) after 3 and 6 d of treatment with paracetamol, respectively. Safety profiles of paracetamol and ibuprofen are similar. Meta-analysis demonstrated an efficacy of paracetamol comparable with that reported for ibuprofen. Efficacy of paracetamol seems to depend on GA and postnatal age of neonate and on modalities of drug administration[45].

The Cochrane review[57] which compared the effectiveness and safety of paracetamol versus ibuprofen combined two studies with 250 preterm infants in total. The success rate for paracetamol in ductal closure was similar to that of ibuprofen in addition to similar adverse events. However, infants who were treated with paracetamol had a lower risk of hyperbilirubinaemia than those treated with ibuprofen. Data on adverse effects on the developing brain from paracetamol in an experimental study and an association between prenatal paracetamol and the development of autism or autism spectrum disorder in childhood limits its wide use. Since no long term follow-up data are vailable for paracetamol use, it can not be recommended as the first line treatment choice.

**CONCLUSION**

Regarding to the management of PDA in preterm neonates, neonatologists and cardiologists have not reached a consensus on which PDAs to treat, when to treat, and how to treat. Currently, more neonates are managed conservatively, and the number of infants receiving surgical ligation is declining; however, there is a need for RCTs concerning the effect of this approach on long-term cardiovascular, pulmonary, and neurodevelopmental health.

Ibuprofen seems to be the first choice due to its higher safety profile, as it is associated with fewer gastrointestinal and renal side effects when compared to indomethacin. PDA closure rates are better with oral than with intravenous ibuprofen. Indomethacin and ibuprofen remain the mainstays of medical management, whereas acetaminophen use is emerging as a less toxic option. Recent studies suggest that paracetamol can be an alternative in the management of PDA with similar efficacy but lower side events than NSAIDs.

The summaries of the some of the studies about oral ibuprofen and paracetamol are shown in Table 1. Considering the potential adverse effects of drugs, a careful monitoring including feeding intolerance, abdominal distension, oliguria and hypertension, and laboratory evaluation for renal and hepatic side effects in case of any need during and following day after the treatment is highly recommended. However, safety evaluation should also always consider long-term consequences of clinical and subclinical side effects. Comparison of adverse effects of oral ibuprofen and paracetamol are summarized in Table 2. Safety should be investigated especially in extreme preterm infants before routine use of paracetamol for PDA closure. We suggest that further prospective, randomized controlled trials are needed to evaluate the efficacy of oral versus intravenous paracetamol or intravenous paracetamol versus intravenous ibuprofen/indomethacin for the closure of PDA.

**REFERENCES**

1 **Mouzinho AI**, Rosenfeld CR, Risser R. Symptomatic patent ductus arteriosus in very-low-birth-weight infants: 1987-1989. *Early Hum Dev* 1991; **27**: 65-77 [PMID: 1802665 DOI: 10.1016/0378-3782(91)90028-2]

2 **Reller MD**, Rice MJ, McDonald RW. Review of studies evaluating ductal patency in the premature infant. *J Pediatr* 1993; **122**: S59-S62 [PMID: 8501549 DOI: 10.1016/S0022-3476(09)90044-0]

3 **Oncel MY**, Erdeve O. Safety of therapeutics used in management of patent ductus arteriosus in preterm infants. *Curr Drug Saf* 2015; **10**: 106-112 [PMID: 25323589 DOI: 10.2174/1574886309999141030142847]

4 **Van Overmeire B**, Chemtob S. The pharmacologic closure of the patent ductus arteriosus. *Semin Fetal Neonatal Med* 2005; **10**: 177-184 [PMID: 15701582 DOI: 10.1016/j.siny.2004.10.003]

5 **Clyman RI**. Mechanisms regulating the ductus arteriosus. *Biol Neonate* 2006; **89**: 330-335 [PMID: 16770073 DOI: 10.1159/000092870]

6 **Graham GG**, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013; **21**: 201-232 [PMID: 23719833 DOI: 10.1007/s10787-013-0172-x]

7 **Fowlie PW**, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev* 2010; **(7)**: CD000174 [PMID: 20614421 DOI: 10.1002/14651858.CD000174]

8 **Ohlsson A**, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2010; **(4)**: CD003481 [PMID: 20393936 DOI: 10.1002/14651858.CD003481.pub4]

9 **Demirel G**, Erdeve O, Dilmen U. Pharmacological Management of PDA: oral versus intravenous medications. *Curr Clin Pharmacol* 2012; **7**: 263-270 [PMID: 22794156 DOI: 10.2174/157488412803305830]

10 **Gokmen T**, Erdeve O, Altug N, Oguz SS, Uras N, Dilmen U. Efficacy and safety of oral versus intravenous ibuprofen in very low birth weight preterm infants with patent ductus arteriosus. *J Pediatr* 2011; **158**: 549-554.e1 [PMID: 21094951 DOI: 10.1016/j.jpeds.2010.10.008]

11 **Erdeve O**, Yurttutan S, Altug N, Ozdemir R, Gokmen T, Dilmen U, Oguz SS, Uras N. Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2012; **97**: F279-F283 [PMID: 22147286 DOI: 10.1136/archdischild-2011-300532]

12 **Clyman RI**, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin Perinatol* 2012; **36**: 123-129 [PMID: 22414883 DOI: 10.1053/j.semperi.2011.09.022]

13 **Erdeve O**, Sarici SU, Sari E, Gok F. Oral-ibuprofen-induced acute renal failure in a preterm infant. *Pediatr Nephrol* 2008; **23**: 1565-1567 [PMID: 18446376 DOI: 10.1007/s00467-008-0835-9]

14 **Allegaert K**, Anderson B, Simons S, van Overmeire B. Paracetamol to induce ductus arteriosus closure: is it valid? *Arch Dis Child* 2013; **98**: 462-466 [PMID: 23606713 DOI: 10.1136/archdischild-2013-303688]

15 **Grèen K**, Drvota V, Vesterqvist O. Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). *Prostaglandins* 1989; **37**: 311-315 [PMID: 2664901 DOI: 10.1016/0090-6980(89)90001-4]

16 **Lucas R**, Warner TD, Vojnovic I, Mitchell JA. Cellular mechanisms of acetaminophen: role of cyclo-oxygenase. *FASEB J* 2005; **19**: 635-637 [PMID: 15705740 DOI: 10.1096/fj.04-2437fje]

17 **Hammerman C**, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. *Pediatrics* 2011; **128**: e1618-e1621 [PMID: 22065264 DOI: 10.1542/peds.2011-0359]

18 **Oncel MY**, Yurttutan S, Uras N, Altug N, Ozdemir R, Ekmen S, Erdeve O, Dilmen U. An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F94 [PMID: 22611117 DOI: 10.1136/archdischild-2012-302044]

19 **Oncel MY**, Yurttutan S, Degirmencioglu H, Uras N, Altug N, Erdeve O, Dilmen U. Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. *Neonatology* 2013; **103**: 166-169 [PMID: 23258386 DOI: 10.1159/000345337]

20 **Yurttutan S**, Oncel MY, Arayicı S, Uras N, Altug N, Erdeve O, Dilmen U. A different first-choice drug in the medical management of patent ductus arteriosus: oral paracetamol. *J Matern Fetal Neonatal Med* 2013; **26**: 825-827 [PMID: 23205872 DOI: 10.3109/14767058.2012.755162]

21 **Oncel MY**, Yurttutan S, Erdeve O, Uras N, Altug N, Oguz SS, Canpolat FE, Dilmen U. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. *J Pediatr* 2014; **164**: 510-4.e1 [PMID: 24359938 DOI: 10.1016/j.jpeds.2013.11.008]

22 **Mosca F**, Bray M, Lattanzio M, Fumagalli M, Tosetto C. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. *J Pediatr* 1997; **131**: 549-554 [PMID: 9386657 DOI: 10.1016/S0022-3476(97)70060-X]

23 **Romagnoli C**, De Carolis MP, Papacci P, Polimeni V, Luciano R, Piersigilli F, Delogu AB, Tortorolo G. Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates. *Clin Pharmacol Ther* 2000; **67**: 676-683 [PMID: 10872650 DOI: 10.1067/mcp.2000.107048]

24 **Pezzati M**, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. *J Pediatr* 1999; **135**: 733-738 [PMID: 10586177 DOI: 10.1016/S0022-3476(99)70093-4]

25 **Aranda JV**, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, Papageorgiou A, Chemtob S. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. *Acta Paediatr* 1997; **86**: 289-293 [PMID: 9099319 DOI: 10.1111/j.1651-2227.1997.tb08892.x]

26 **Desfrere L**, Zohar S, Morville P, Brunhes A, Chevret S, Pons G, Moriette G, Rey E, Treluyer JM. Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method. *J Clin Pharm Ther* 2005; **30**: 121-132 [PMID: 15811164 DOI: 10.1111/j.1365-2710.2005.00630.x]

27 **Yurttutan S**, Erdeve O, Oncel MY, Ozdemir R, Dilmen U. The relationship between trough drug concentrations and ductal closure in preterm infants treated with three-dose-oral ibuprofen. *J Matern Fetal Neonatal Med* 2013; **26**: 1306-1310 [PMID: 23488980 DOI: 10.3109/14767058.2013.784739]

28 **Ohlsson A**, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2011; **(7)**: CD004213 [PMID: 21735396 DOI: 10.1002/14651858.CD004213.pub3]

29 **Kanmaz G**, Erdeve O, Canpolat FE, Oğuz SS, Uras N, Altug N, Greijdanus B, Dilmen U. Serum ibuprofen levels of extremely preterm infants treated prophylactically with oral ibuprofen to prevent patent ductus arteriosus. *Eur J Clin Pharmacol* 2013; **69**: 1075-1081 [PMID: 23128963 DOI: 10.1007/s00228-012-1438-8]

30 **Aly H**, Lotfy W, Badrawi N, Ghawas M, Abdel-Meguid IE, Hammad TA. Oral Ibuprofen and ductus arteriosus in premature infants: a randomized pilot study. *Am J Perinatol* 2007; **24**: 267-270 [PMID: 17484080 DOI: 10.1055/s-2007-976550]

31 **Cherif A**, Khrouf N, Jabnoun S, Mokrani C, Amara MB, Guellouze N, Kacem S. Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. *Pediatrics* 2008; **122**: e1256-e1261 [PMID: 19047225 DOI: 10.1542/peds.2008-1780]

32 **Neumann R**, Schulzke SM, Bührer C. 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; **102**: 9-15 [PMID: 22414850 DOI: 10.1159/000335332]

33 **Austin N**, Cleminson J, Darlow BA, McGuire W. Prophylactic oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. *Cochrane Database Syst Rev* 2015; **10**: CD003478 [PMID: 26497202 DOI: 10.1002/14651858.CD003478.pub5]

34 **Peng S**, Duggan A. Gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Expert Opin Drug Saf* 2005; **4**: 157-169 [PMID: 15794710 DOI: 10.1517/14740338.4.2.157]

35 **Tatli MM**, Kumral A, Duman N, Demir K, Gurcu O, Ozkan H. Spontaneous intestinal perforation after oral ibuprofen treatment of patent ductus arteriosus in two very-low-birthweight infants. *Acta Paediatr* 2004; **93**: 999-1001 [PMID: 15303820 DOI: 10.1111/j.1651-2227.2004.tb02702.x]

36 **Guzoglu N**, Sari FN, Ozdemir R, Oguz SS, Uras N, Altug N, Dilmen U. Renal and mesenteric tissue oxygenation in preterm infants treated with oral ibuprofen. *J Matern Fetal Neonatal Med* 2014; **27**: 197-203 [PMID: 23735121 DOI: 10.3109/14767058.2013.811485]

37 **Ohlsson A**, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2013; **4**: CD003481 [PMID: 23633310 DOI: 10.1002/14651858.CD003481.pub5]

38 **Ahlfors CE**. Effect of ibuprofen on bilirubin-albumin binding. *J Pediatr* 2004; **144**: 386-388 [PMID: 15001951 DOI: 10.1016/j.jpeds.2003.11.027]

39 **Cooper-Peel C**, Brodersen R, Robertson A. Does ibuprofen affect bilirubin-albumin binding in newborn infant serum? *Pharmacol Toxicol* 1996; **79**: 297-299 [PMID: 9000255 DOI: 10.1111/j.1600-0773.1996.tb00012.x]

40 **Zecca E**, Romagnoli C, De Carolis MP, Costa S, Marra R, De Luca D. Does Ibuprofen increase neonatal hyperbilirubinemia? *Pediatrics* 2009; **124**: 480-484 [PMID: 19620202 DOI: 10.1542/peds.2008-2433]

41 **Gournay V**, Savagner C, Thiriez G, Kuster A, Rozé JC. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. *Lancet* 2002; **359**: 1486-1488 [PMID: 11988250 DOI: 10.1016/S0140-6736(02)08424-6]

42 **Keady S**, Grosso A. Ibuprofen in the management of neonatal Patent Ductus Arteriosus. *Intensive Crit Care Nurs* 2005; **21**: 56-58 [PMID: 15681219 DOI: 10.1016/j.iccn.2004.11.002]

43 **O'Brien WF**, Krammer J, O'Leary TD, Mastrogiannis DS. The effect of acetaminophen on prostacyclin production in pregnant women. *Am J Obstet Gynecol* 1993; **168**: 1164-1169 [PMID: 8475962 DOI: 10.1016/0002-9378(93)90362-M]

44 **Dang D**, Wang D, Zhang C, Zhou W, Zhou Q, Wu H. Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial. *PLoS One* 2013; **8**: e77888 [PMID: 24223740 DOI: 10.1371/journal.pone.0077888]

45 **Terrin G**, Conte F, Oncel MY, Scipione A, McNamara PJ, Simons S, Sinha R, Erdeve O, Tekgunduz KS, Dogan M, Kessel I, Hammerman C, Nadir E, Yurttutan S, Jasani B, Alan S, Manguso F, De Curtis M. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2015; Epub ahead of print [PMID: 26283668 DOI: 10.1136/archdischild-2014-307312]

46 **Bouayad A**, Kajino H, Waleh N, Fouron JC, Andelfinger G, Varma DR, Skoll A, Vazquez A, Gobeil F, Clyman RI, Chemtob S. Characterization of PGE2 receptors in fetal and newborn lamb ductus arteriosus. *Am J Physiol Heart Circ Physiol* 2001; **280**: H2342-H2349 [PMID: 11299240 DOI: 10.1038/sj.bjp.0705092]

47 **Tekgunduz KS**, Ceviz N, Demirelli Y, Olgun H, Caner I, Sahin IO, Yolcu C. Intravenous paracetamol for patent ductus arteriosus in premature infants - a lower dose is also effective. Concerning the article by M.Y. Oncel et al: Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants [Neonatology 2013; 103: 166-169]. *Neonatology* 2013; **104**: 6-7 [PMID: 23548678 DOI: 10.1159/000348568]

48 **Alan S**, Kahvecioglu D, Erdeve O, Atasay B, Arsan S. Is paracetamol a useful treatment for ibuprofen-resistant patent ductus arteriosus?. Concerning the article by M.Y. Oncel et al: intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants [Neonatology 2013; 103: 166-169]. *Neonatology* 2013; **104**: 168-169 [PMID: 23921529 DOI: 10.1159/000352068]

49 **Dart RC**, Rumack BH. Intravenous acetaminophen in the United States: iatrogenic dosing errors. *Pediatrics* 2012; **129**: 349-353 [PMID: 22271694 DOI: 10.1542/peds.2011-2345]

50 **Nevin DG**, Shung J. Intravenous paracetamol overdose in a preterm infant during anesthesia. *Paediatr Anaesth* 2010; **20**: 105-107 [PMID: 20078803 DOI: 10.1111/j.1460-9592.2009.03210.x]

51 **Isbister GK**, Bucens IK, Whyte IM. Paracetamol overdose in a preterm neonate. *Arch Dis Child Fetal Neonatal Ed* 2001; **85**: F70-F72 [PMID: 11420329 DOI: 10.1136/fn.85.1.F70]

52 **Porta R**, Sánchez L, Nicolás M, García C, Martínez M. Lack of toxicity after paracetamol overdose in a extremely preterm neonate. *Eur J Clin Pharmacol* 2012; **68**: 901-902 [PMID: 22227961 DOI: 10.1007/s00228-011-1165-6]

53 **Anderson BJ**, Allegaert K. Intravenous neonatal paracetamol dosing: the magic of 10 days. *Paediatr Anaesth* 2009; **19**: 289-295 [PMID: 19335341 DOI: 10.1111/j.1460-9592.2008.02680.x]

54 **Palmer GM**, Atkins M, Anderson BJ, Smith KR, Culnane TJ, McNally CM, Perkins EJ, Chalkiadis GA, Hunt RW. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* 2008; **101**: 523-530 [PMID: 18628265 DOI: 10.1093/bja/aen208]

55 **Beringer RM**, Thompson JP, Parry S, Stoddart PA. Intravenous paracetamol overdose: two case reports and a change to national treatment guidelines. *Arch Dis Child* 2011; **96**: 307-308 [PMID: 21127004 DOI: 10.1136/adc.2010.192005]

56 **Kratz A**, Ferraro M, Sluss PM, Lewandrowski KB. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. *N Engl J Med* 2004; **351**: 1548-1563 [PMID: 15470219 DOI: 10.1056/NEJMcpc049016]

57 **Ohlsson A**, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants. *Cochrane Database Syst Rev* 2015; **3**: CD010061 [PMID: 25758061 DOI: 10.1002/14651858.CD010061.pub2]

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**Table 1 Summary of the studies comparing oral ibuprofen and others (IV ibuprofen/indomethacin, oral paracetamol)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Comparison (n)** | **Gestational age (wk)** | **Method** | **Ductal closure rates** | **Comparison of adverse effects** | **Conclusion** |
| Aly *et al*[30](LOE 1A) | IV INDO (9)Oral IBU (12) | IV INDO: 32.9 ± 1.6Oral IBU: 31.2 ± 2.5 | Prospective,randomized,single mask | Oral IBU | IV INDO | Oral IBU = IV INDO | Oral IBU could be an easy to administer and efficacious alternative treatment. |
| 83% | 78% |
| Cherif *et al*[31](LOE 1A) | IV IBU (32)Oral IBU (32) | IV IBU: 28.3 ± 1.1Oral IBU: 29.3 ± 1.2 | Prospective,randomized,single mask | Oral IBU | IV IBU | Oral IBU < IV IBU | Early ductal closure with oral IBU is as good as IV route |
| 70.3% | 70% |
| Gokmen *et al*[10](LOE 1A) | IV IBU (50)Oral IBU (52) | IV IBU: 28.7 ± 2.1Oral IBU: 28.5 ± 1.9 | Prospective,randomized | Oral IBU | IV IBU | IV IBU = Oral IBU | Oral IBU is more effective than IV IBU for ductal closure in VLBW infants |
| 84.6%1 | %62 |
| Erdeve *et al*[11](LOE 1A) | IV IBU (34)Oral IBU (36) | IV IBU: 26.3 ± 1.3Oral IBU: 26.4 ± 1.1 | Prospective,randomized | Oral IBU | IV IBU | BPD is lower with oral IBU | Oral IBU is as effective as IV IBU for PDA closure even in < 1000 g preterm infants. |
| 83.3%1 | 61.7% |
| Dang *et al*[42](LOE 1B) | Oral PARA (80)Oral IBU (80) | Oral PARA: 31.2 ± 1.8Oral IBU: 30.9 ± 2.2 | Prospective,randomized | Oral PARA | Oral IBU | Oral PARA < Oral IBU | Oral PARA was comparable to IBU in terms of the rate of ductal closure and even showed a decreased risk of hyperbilirubinemia or gastrointestinal bleeding. |
| 81.2% | 78.8% |
| Oncel *et al*[21](LOE 1B) | Oral PARA (40)Oral IBU (40) | Oral PARA: 27.3 ± 1.7Oral IBU: 27.3 ± 2.1 | Prospective,randomized | Oral PARA | Oral IBU | Oral PARA = Oral IBU | Oral PARA is as effective as oral IBU for PDA closure. |
| 72.5% | 77.5% |

LOE: Levels of evidence; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; PARA: Paracetamol; PDA: Patent ductus arteriosus; BPD: Bronchopulmonary dysplasia. 1Differences were statistically significant (*P* < 0.05).

**Table 2 Comparison of adverse effects of oral ibuprofen and paracetamol[3]**

|  |  |  |
| --- | --- | --- |
|  | **Oral ibuprofen**  | **Oral paracetamol** |
| Renal side effects | +/- | - |
| NEC | + | - |
| Spontaneous intestinal perforation | + | - |
| Gastrointestinal system bleeding | ++ | - |
| IVH | + | - |
| BPD | +/- | - |
| Alteration of platelet function | + | - |
| Decrease in cerebral blood flow | - | - |
| Hyperbilirubinemia | +/- | - |
| Hypertransaminasemia | - | + |

NEC: Necrotizing enterocolitis; IVH: Intraventricular hemorrhage; BPD: Bronchopulmonary dysplasia.