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MINIREVIEWS

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

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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

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-H_2 synthetase (PGHS) enzyme system, which has two active sites as cyclo-oxygenase (COX) and peroxidase (POX), produces circulating prostaglandins 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 *vs* oral paracetamol in a non-blinded trial. Overall closure rates were similar at 79% *vs* 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 wk)[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.

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 ± 1.6 Oral IBU: 31.2 ± 2.5	Prospective, randomized, single mask	Oral IBU 83%	IV INDO 78%	Oral IBU = IV INDO	Oral IBU could be an easy to administer and efficacious alternative treatment.
Cherif *et al*[31] (LOE 1A)	IV IBU (32) Oral IBU (32)	IV IBU: 28.3 ± 1.1 Oral IBU: 29.3 ± 1.2	Prospective, randomized, single mask	Oral IBU 70.30%	IV IBU 70%	Oral IBU < IV IBU	Early ductal closure with oral IBU is as good as IV route
Gokmen *et al*[10] (LOE 1A)	IV IBU (50) Oral IBU (52)	IV IBU: 28.7 ± 2.1 Oral IBU: 28.5 ± 1.9	Prospective, randomized	Oral IBU 84.6%[1]	IV IBU 62%	IV IBU = Oral IBU	Oral IBU is more effective than IV IBU for ductal closure in VLBW infants
Erdeve *et al*[11] (LOE 1A)	IV IBU (34) Oral IBU (36)	IV IBU: 26.3 ± 1.3 Oral IBU: 26.4 ± 1.1	Prospective, randomized	Oral IBU 83.3%[1]	IV IBU 61.70%	BPD is lower with oral IBU	Oral IBU is as effective as IV IBU for PDA closure even in < 1000 g preterm infants.
Keady *et al*[42] (LOE 1B)	Oral PARA (80) Oral IBU (80)	Oral PARA: 31.2 ± 1.8 Oral IBU: 30.9 ± 2.2	Prospective, randomized	Oral PARA 81.20%	Oral IBU 78.80%	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.
Oncel *et al*[21] (LOE 1B)	Oral PARA (40) Oral IBU (40)	Oral PARA: 27.3 ± 1.7 Oral IBU: 27.3 ± 2.1	Prospective, randomized	Oral PARA 72.50%	Oral IBU 77.50%	Oral PARA = Oral IBU	Oral PARA is as effective as oral IBU for PDA closure.

[1]Differences were statistically significant ($P < 0.05$). LOE: Levels of evidence; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; PARA: Paracetamol; PDA: Patent ductus arteriosus; BPD: Bronchopulmonary dysplasia; VLBW: Very low birth weight.

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.

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 *vs* 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 available 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 *vs* intravenous paracetamol or intravenous paracetamol *vs* intravenous ibuprofen/indomethacin for the closure of PDA.

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