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Original Article

Patent ductus arteriosus treatment in preterm neonates, which is the drug of choice paracetamol vs ibuprofen?

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Abstract

Background
Patent ductus arteriosus (PDA) is one of the most prevalent problems in preterm infants. Although ibuprofen represents one of the choices for the closure of PDA, this treatment can cause severe gastrointestinal and adverse renal effects and worsen platelet function. Effective therapy for PDA had been suggested as paracetamol.

Aim
Our study is aiming to compare the efficacy and safety of paracetamol and ibuprofen.

Patients and methods
A prospective observational, single-center study was performed from December 2016 until August 2017, at ElGalaa Teaching Hospital in Cairo. In this study we included neonates with a gestational age of 28–36 weeks, diagnosed with a significant hemodynamically PDA using clinical and ultrasonographic cardiac evaluation. The pediatric cardiologist performed an echocardiographic examination before the start of the treatment and after seven days.

Results
We found that paracetamol had good efficacy on PDA in preterm infants, and the closure rate of paracetamol was comparable to that of ibuprofen.

Conclusion
Paracetamol may confer comparable treatment efficacy for the closure of PDA to ibuprofen, although paracetamol is associated with lower risk of adverse events.

Keywords: Echocardiography, ibuprofen, paracetamol, patent ductus arteriosus

Introduction

One of the common cardiovascular problems that prematurely born infants experience early in life is patent ductus arteriosus (PDA). PDA is a blood vessel that connects the aorta and the pulmonary artery. PDA is essential in maintaining circulation in fetal life [1]. After the delivery of the baby, fetal circulation changes to adult circulation. Moreover, within 18–24 h of life, the ductus arteriosus (DA) functionally closes [1]. On the contrary, in babies born prematurely, the DA often fails to close spontaneously and leads to some morbidities. It has been shown that in infants born with a birth weight of less than 1000 g, the DA remains open in 66% of infants beyond the first week of life. In the extreme premature population born at 24 weeks of gestation, only 13% of infants were found to have their ductus closed by the end of the first week [2]. Although the ductus remains open, blood typically flows left-to-right from the aorta into the pulmonary artery. As pulmonary vascular resistance decreases within the first several days after birth, the diverted aortic blood flow into the pulmonary circulation correspondingly increases. This is named as 'ductal steal,' which results in excessive blood flow through the lungs, predisposing to the development of pulmonary congestion, pulmonary edema, and

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worsening respiratory failure. Diversion of blood flow from the systemic circulation may exceed capabilities for compensatory increases in total cardiac output. This increase in the cardiac output results in compromised perfusion of vital organs, including bowel, kidney, and brain [3]. This condition PDA is associated with a prolonged ventilation need and carries an increased risk of morbidity [i.e. necrotizing enterocolitis (NEC), chronic lung disease] and even mortality [4–6]. For the diagnosis of PDA echocardiography is the procedure of choice; it classifies the PDA as silent, small, moderate, or large [7]. Hemodynamically significant PDA (hsPDA) is diagnosed when there is left atrium-to-aortic root diameter ratio greater than 1.6, DA diameter of greater than 1.5 mm, left ventricular enlargement, and holodiastolic flow reversal in the descending aorta [8] (Table 1).

Pharmacological closure with NSAIDs, mainly ibuprofen and indomethacin, is currently the standard of care [9]. NSAIDs are not effective in ~30% of patients, however, and can have adverse effects such as gastrointestinal bleeding and perforation, diminished platelet aggregation, hyperbilirubinemia, and transient renal function impairment [10,11]. Moreover, NSAIDs are contraindicated in a considerable proportion of newborns, notably those with renal failure, intracranial hemorrhage, gastrointestinal problems, and thrombocytopenia. If NSAIDs fail or are contraindicated, the only currently available solution is surgical ligation. The risks of cardiothoracic surgery and impaired neurological outcome make surgical ligation not to be the first choice [12]. Therefore, PDA closure needs another pharmacological intervention. An alternative drug for PDA closure was suggested which is paracetamol [13]. Acetaminophen is another drug that inhibits the activity of prostaglandin synthase in the peroxidase region of the enzyme [14]. Recent studies have shown that acetaminophen can be used to treat PDA in preterm infants with good efficacy and few adverse effects, unlike cyclooxygenase inhibitors [15].

Participants and methods

Ethics committee approval was taken. In a prospective observational, single-center study performed from December 2016 until August 2017, at the NICU ElGalaa Teaching Hospital in Cairo, we included neonates with a gestational age of 28–36 weeks, diagnosed with a hemodynamically significant patent ductus arteriosus (hsPDA) using clinical and cardiac ultrasound evaluation.

In our department, a protocol for PDA treatment was initially by intravenous ibuprofen, a single daily dose for 3 days course (10 mg/kg on the first day, 5 mg/kg on the second and third days). Moreover, if closure was not yet obtained, a repeated 3-day course was given (group A). Paracetamol (Perfalgan; Bristol Myers Squibb Corporate Headquarters, New York, NY 10016) was given if ibuprofen was contraindicated [16]. Intravenous paracetamol 15 mg/kg every 6 h (60 mg/kg/day) was administered for 5 days (group B).

Table 1: Patent ductus arteriosus classification

Types	Size	Murmur present (yes/no)
Silent	<1.5 mm	No
Small	1.5-3 mm	Yes
Moderate	3-5 mm	Yes
Large	>5 mm	Yes

Contraindications for ibuprofen treatment were active intracranial hemorrhage, thrombocytopenia or other known clotting disorders, severe sepsis, suspected or confirmed NEC, intestinal perforation, liver and kidney function disorders (oliguria <1.0 ml/kg/h, serum creatinine >110 μmol/l) and severe hyperbilirubinemia.

The pediatric cardiologist performed an echocardiographic examination before the start of treatment and after seven days. Two-dimensional color Doppler echocardiography was performed using ultrasound system equipped with a 10-MHz transducer.

After fulfillment of the inclusion criteria. Patients will be divided into two groups: ibuprofen group (group A) and paracetamol group (group B). They will start the course of treatment within 24–72 h of age.

If PDA closure is achieved, the patients will have follow-up examinations.

If PDA is still patent and hemodynamically not significant, they will receive follow-up examinations.

If PDA is still open and hemodynamically significant, patients in both groups will be treated with a 3-day course of ibuprofen as a rescue medication.

In case of further failure of pharmacological treatment, the management of PDA (i.e. further pharmacological and surgical treatment) will be performed following the hospital's local protocol.

The early adverse events were defined as those occurring after administration of the drug treatment during and up to 1 week. The safety outcomes of both drugs were observed. This includes early adverse events [e.g. oliguria, emerging intraventricular hemorrhage (IVH), tendency to bleed, NEC, hyperbilirubinemia, and death] and late adverse events, for example, Biparietal diameter (BPD).

Statistical methods

The infants' clinical characteristics in the paracetamol (group A) and ibuprofen (group B) will be described utilizing mean value and SD, median value, and range. Alternatively, frequencies and percentage were used. A P value less than 0.05 was considered statistically significant.

Results

Efficacy of treatment

The ductus was closed in 48 (87.2%) infants of the paracetamol group compared with 43 (78.1%) of the ibuprofen group,

Table 2: Baseline characteristics of study patients

	Group A (*n*=55)	Group B (*n*=55)	*P*
Gestational age (weeks) (median)	31.6 (2.3)	32.4 (2.24)	0.474
Weight (g)	1867 (453.5)	1905 (348.6)	0.342
Sex			
Male	28	34	0.32
Female	27	21	
Mode of delivery [*n* (%)]			
CS	33 (4.5)	29 (2.1)	0.447
Vaginal	22 (5.1)	26 (6.3)	
Age in days	2.85 (1.28)	3.42 (2.12)	0.54

No significant differences were detected between infants of group A and group B regarding their essential characteristics. CS, cesarean section. $P<0.05$ is significant

Table 3: Number of days to ductal closure

	Group A (*n*=55)	Group B (*n*=55)	*P*
PDA before start (mm) (median)	2.7	3.3	0.459
PDA after 7 days (mm) (median)	1.7	2	0.103
Closure rate (*n*/%)	43/78.1	48/82.7	0.69
Mean days needed for closure	3.71±0.16	3.22±0.14	0.02

PDA, patent ductus arteriosus. $P<0.05$ is significant.

Table 4: Safety profiles for paracetamol and ibuprofen treatments

	Group A (*n*=55)	Group B (*n*=55)	*P*
Oliguria	4	3	0.42
Renal failure	1	0	0.32
NEC	1	2	0.73
Hyperbilirubinemia	28	16	0.03
GIT bleeding	4	1	0.01
IVH	3	3	1
BPD	3	2	0.77

GIT, gastrointestinal tract; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis. $P<0.05$ is significant.

and there was no significant difference between the two groups ($P=0.693$) (Table 2). However, mean days for closure were significantly less in the group that received paracetamol (Table 3).

Safety profiles of paracetamol and ibuprofen treatments

No significant differences were detected between infants of group A and group B in the incidence of oliguria, renal failure, NEC, BPD, and IVH grade. However, significant differences in the incidence rates of gastrointestinal bleeding and hyperbilirubinemia were detected between the two groups ($P < 0.05$) (Table 4).

Discussion

There is a debate about the proper timing of the pharmacological treatment of PDA in preterm newborns. The clinical practice in different centers widely varies [16]. Early treatment may have a beneficial effect on early PDA-related morbidity, whereas late, delayed treatment prevents overtreatment in those cases of spontaneously closing PDA [17]. Recent data suggest that early ibuprofen treatment of PDA at a median age of 3 days does not significantly affect the occurrence of death or NEC, BPD, severe IVH, and PVL, in comparison with a delayed treatment at the median age of 11 days in the newborn of 23–32 weeks of gestation. This suggests that late treatment is safe and more favorable regarding overtreatment reduction [18]. It has been reported that the spontaneous closure of 49% of all PDA occurs within the first week in newborns with birth weight less than 1500 g and in 94% of newborns before discharge, suggesting that deferring treatment decisions until at least 1 week of life may avoid unnecessary treatment exposure [18].

We found that paracetamol had good efficacy on PDA in preterm infants, and the closure rate of paracetamol was comparable to that of ibuprofen. Furthermore, the mean number of days to ductal closure was shorter in the paracetamol group than in the ibuprofen group (3.22 ± 0.14 vs 3.71 ± 0.16 days, $P=0.020$). This indicates that paracetamol can treat PDA more rapidly compared with ibuprofen. Therefore, paracetamol is better suited for severe cases in which quick relief of symptoms is needed. Ductal closure in newborns is known to be dependent on increased blood oxygen and decreased vasodilators, including prostaglandin E2 and I2 [19]. Dang *et al.* [11], found overall, PDA closure occurred in 65 (81.2%) patients in the paracetamol group and 63 (78.8%) patients in the ibuprofen group ($P=0.693$). However, Oncel *et al.* [20] found that after the first treatment course, the PDA closed in 29 (72.5%) patients in the paracetamol group vs 31 (77.5%) patients in the ibuprofen group ($P=0.6$). Roofthooft *et al.* [21] found limited effects of intravenous paracetamol on PDA in very low-birth-weight infants with contraindications for ibuprofen or after ibuprofen failure.

Finally, the incidence rates were significantly lower for gastrointestinal bleeding and hyperbilirubinemia in the paracetamol group than those of the ibuprofen group. Ibuprofen is 99% protein bound, and at higher concentrations, it can be a competitive displacer of bilirubin for albumin-binding sites, thereby potentially increasing the risk of hyperbilirubinemia [22,23]. Moreover, two studies have demonstrated that ibuprofen treatment results in higher peak levels of total serum bilirubin and longer durations of phototherapy [24,25]. So, paracetamol may be indicated for PDA in preterm infants with hyperbilirubinemia. Moreover, Dang *et al.* [11] found that paracetamol may be used as the drug of choice for PDA in preterm infants with good efficacy and lower risk of gastrointestinal bleeding or hyperbilirubinemia compared with ibuprofen treatment.

Conclusion

In conclusion, we have demonstrated in this trial that paracetamol may be utilized as the drug of choice for PDA in preterm infants with good efficacy, and lower risk of gastrointestinal bleeding or hyperbilirubinemia compared with ibuprofen treatment and is especially suited for those with hyperbilirubinemia.

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Conflicts of interest

There are no conflicts of interest.

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