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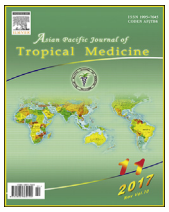

Original research https://doi.org/10.1016/j.apjtm.2017.10.012

Oral pharmacological treatment for patent ductus arteriosus in premature neonates with hemodynamic repercussions

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ARTICLE INFO

Article history:
Received 18 Aug 2017
Received in revised form 29 Aug 2017
Accepted 16 Sep 2017
Available online 28 Oct 2017

Keywords:
Patent ductus arteriosus
Premature neonatal
Indomethacin
Ibuprofen
Paracetamol

ABSTRACT

Objective: To evaluate the efficacy of oral indomethacin, ibuprofen, and paracetamol in oral dosage form on patent ductus arteriosus (PDA) in premature neonates with significant clinical and hemodynamic repercussions (CHRs) and to determine the effect of these respective treatments on renal function.

Methods: A retrospective study of cases of PDA in premature neonates in the Neonatal Intensive Care Unit was conducted. The treatments consisted of indomethacin [0.2 mg/(kg·d), 3-day cycle], ibuprofen [10 mg/(kg·d) followed by 5 mg/(kg·d), 3-day cycle], and paracetamol (15 mg/kg every 6 h, 5-day cycle). The drugs were administered as an oral solution. The following variables were considered: gestational age, newborn weight at birth, Apgar score, diuresis, serum creatinine and urea levels, and serum electrolyte levels (sodium and potassium).

Results: Treatment with indomethacin presented efficacy of 87.5% in closure of the ductus with a mean outcome period of 3.5 d. In premature neonates with CHRs and contraindications for indomethacin, the initial treatment with either ibuprofen or paracetamol failed to close the ductus. However, when this treatment was followed by indomethacin, closure occurred in 66.7% of the neonates, with an outcome period of 9.66 d. The initial treatment with one cycle of ibuprofen followed by one or two cycles of paracetamol failed to close the ductus.

Conclusions: Oral indomethacin was effective for closure of the PDA in premature neonates with severe CHRs. Oral paracetamol or ibuprofen for PDA closure in premature neonates with severe CHRs and contraindications for indomethacin was ineffective. However, results in clinical improvements of neonates allowed the subsequent use of indomethacin and successful closure of the ductus. A significant reduction of diuresis occurred in neonates who were treated with indomethacin, either as a first-line treatment or after the failure of ibuprofen or paracetamol.

1. Introduction

Patent ductus arteriosus (PDA) is a common problem in preterm infants. It has been interpreted for decades as a pathological condition that should be readily prevented or treated [1–4]. Questions have been raised about the significance of PDA in preterm neonates (e.g., whether it is a physiological manifestation of extreme prematurity with a high probability of spontaneous closure or whether it is a pathological phenomenon that requires pharmacological or surgical treatment) [4,5].

Patent ductus arteriosus can occur in up to 2/3 of infants who are less than 28 weeks of gestational age. However, spontaneous closure of the ductus will occur only in approximately 34% of these neonates [6]. The clinical condition is nonspecific, especially in the first days of life. The gold standard for the diagnosis of PDA is Doppler echocardiography [4].

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Peer review under responsibility of Hainan Medical University.

Pharmacological treatment with cyclooxygenase-1 and -2 inhibitors is the first-line treatment because they inhibit the production of prostaglandins, which play a key role in persistence of the ductus arteriosus in the first period of life [7,8]. Although indomethacin has been conventionally used for treatment since the 1970s [1,2,9], ibuprofen is also being used as an alternative for closure of the ductus arteriosus [10–13]. More recently, some authors have suggested the use of paracetamol, an inhibitor of prostaglandin H_2 synthase peroxidase activity, as a safe and effective alternative for the treatment of PDA [14–16]. Because of different mechanisms of action, indomethacin has more serious adverse effects than ibuprofen and paracetamol when used for the treatment of PDA [16,17].

Although several studies have investigated this topic, no consensus was been reached regarding the best clinical treatment for PDA in preterm infants with clinical and hemodynamic repercussions (CHR) and contraindications for indomethacin. This justifies the need for further clinical and comparative studies to obtain data on both drug efficacy and safety when used for PDA closure. Additionally, most previous studies were conducted using drugs in intravenous dosage form, which are unavailable in some countries, including Brazil.

Thus, the goals of the present study were to evaluate the efficacy of indomethacin, ibuprofen, and paracetamol in oral dosage form for the treatment of PDA in preterm neonates with significant CHRs and determine the effects of these treatments on renal function.

2. Material and methods

This retrospective study was conducted from January 2015 to January 2016. We reported a series of cases of 12 premature neonates with PDA with CHRs in the Neonatal Intensive Care Unit. Table 1 shows the clinical characteristics of the total population of premature neonates who were evaluated.

All of the neonates were evaluated after the 3rd day of life to detect the presence of PDA using the following clinical criteria: persistent tachycardia, active precordium, wide pulses, hepatomegaly, pulmonary hemorrhage, progressive need for mechanical ventilation, cardiomegaly, and pulmonary congestion on chest X-ray. Echocardiographic criteria were also used, including the presence of a ductus > 1.5 mm, left atrium/aortic root ratio > 1.5 and/or left/right shunt, and reversed end-diastolic flow in the aorta [16].

The treatment regimens were the following: indomethacin [0.2 mg/(kg·d), 3-day cycle], ibuprofen [10 mg/(kg·d) followed by 5 mg/(kg·d), 3-day cycle], and paracetamol (15 mg/kg every 6 h, 5-day cycle). The drugs were administered in oral solution followed by administration of 0.5 mL of distilled water.

Among the premature neonates with PDA, immediately after diagnosis, 66.7% were treated with indomethacin, 25.0% were treated with paracetamol or ibuprofen followed by indomethacin, and 8.3% were treated with ibuprofen followed by paracetamol. The choice of initial treatment with ibuprofen or paracetamol in this case series was based on a diagnosis of oliguria [diuresis < 1 mL/(kg·h)] or abnormal renal function (creatinine > 2.5 mg/dL), active bleeding, coagulation disorders, or thrombocytopenia in four premature infants, contraindicating the use of indomethacin [18].

The following variables were evaluated: gestational age, infant weight at birth, Apgar score in the first 5 min of life, diuresis, serum creatinine and urea levels, and serum electrolyte levels (sodium and potassium). Treatment efficacy was defined by the PDA closure rate by repeated echocardiography, and the outcome period was recorded.

The study was approved by the Permanent Research Ethics Committee involving Human Beings/UEM (Opinion 919203, Dec 2014). The data were analyzed using Fisher's test. Values of $P < 0.05$ were considered statistically significant.

3. Results

Of eight preterm neonates who were treated with indomethacin, only one (12.5%) presented no closure of the ductus arteriosus, which was followed by another cycle of indomethacin and surgical ligation. The median initial diameter of the ductus in these eight infants was 2.1 mm (1.5–3.0 mm). In these neonates, treatment with indomethacin had an efficacy of 87.5% for closure of the ductus, with a mean outcome period of 3.5 d after the initiation of treatment.

In premature neonates with CHRs and contraindications for indomethacin, initial treatment with a cycle of ibuprofen (3 d) or paracetamol (5 d) failed to close the ductus (median initial diameter = 2.5 mm; range = 1.5–3.0 mm). However, when this treatment was followed by one or two cycles of indomethacin, ductus closure occurred in 66.7% of the neonates. The outcome period was 9.66 d after the initiation of treatment.

In preterm neonates with CHRs and contraindications for indomethacin, initial treatment with one cycle of ibuprofen

Table 1
Clinical characteristics of the preterm neonates with hemodynamic repercussions.

Variable	Indomethacin	Paracetamol or ibuprofen + Indomethacin	Ibuprofen + Paracetamol
Gestational age (weeks)	28.37 ± 1.00	30.67 ± 1.40	29.00 ± 1.00
≤ 28	62.50%	33.30%	0%
> 28	37.50%	66.70%	100.00%
Weight at birth (g)	1333 ± 185	1290 ± 70	1155 ± 00
≤ 1000 g	50%	0%	0%
> 1000 g	50%	100%	100%
Apgar score (min)			
0	6.37 ± 0.49	5.66 ± 0.91	5.00 ± 0.82
5	8.62 ± 0.26	8.00 ± 0.36	8.50 ± 0.30
Drug administration period (d)	2.0–6.0	7.0–11.0	8.0
Outcome period (d)	3.50 ± 0.59	9.66 ± 1.30*	_

The data are expressed as the mean ± standard error of the mean of the samples of each group. *Fisher's test ($P < 0.05$).

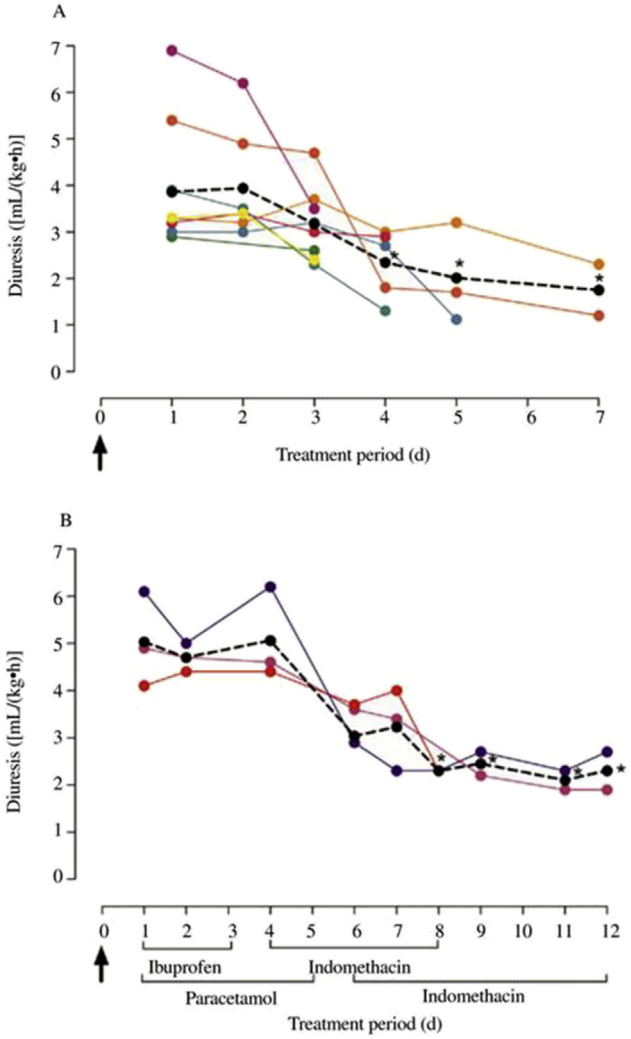

Figure 1. Diuresis of preterm neonates with hemodynamic repercussions. [A]: treated neonates with indomethacin (n = 8). [B]: treated neonates with ibuprofen + indomethacin or paracetamol + indomethacin (n = 3). The dashed curve represents the mean ± SEM of neonates from each group. Each solid line represents a preterm neonate studied. The arrow indicates the beginning of treatment. *P < 0.05 when compared to the period of initiation of indomethacin treatment (Fisher's test).

followed by one or two cycles of paracetamol failed to close the ductus. These neonates then underwent surgical ligation.

Additionally, serum levels of creatinine, urea, and electrolytes did not vary significantly, regardless of the therapeutic regimen that was used (data not shown). However, a significant reduction of diuresis, which indicates acute renal dysfunction, was observed in neonates who were treated with indomethacin, either as a first-line treatment or adjunct treatment after the failure of ibuprofen or paracetamol (Figure 1).

4. Discussion

The ductus arteriosus is a vascular connection functioning as a prenatal bypass between the pulmonary artery and aorta. After birth, the ductus usually closes within the first 48–72 h of life in full-term infants [11,19,20]. In preterm infants, the closure of ductus arteriosus may be delayed or fail to occur due to the mal-development of arterial wall and the secretion of prostaglandin in excess [20,21], which play a key role in persistence of the ductus arteriosus [7,8].

The treatment to close PDA involves the use of cyclooxygenase (COX) inhibitors (indomethacin, ibuprofen or paracetamol) because they inhibit the production of prostaglandins. Some authors reported that indomethacin is one of the most effective drugs for the treatment of PDA, although it can cause adverse effects [16–18,22–25]. Treatment with ibuprofen and paracetamol has been recommended due its lower adverse effects [10–17]. However, the literature indicates some disagreements about the efficacy of ibuprofen and paracetamol for ductus arteriosus closure [26–29]. The discrepancy appears to be related to various factors, such as dose, route of administration, initiation of treatment, drug pharmacokinetics, neonate weight, gestational age, and morbidity, among others [30–38]. These studies corroborate our findings showing a higher efficacy of oral indomethacin compared to ibuprofen and paracetamol.

In our research, ibuprofen and paracetamol were administered because indomethacin was contraindicated, based on oliguria, an increase in creatinine levels > 2.5 mg/dL, and intracranial hemorrhage. In premature neonates with severe CHRs, ibuprofen and paracetamol were ineffective in the closure of the ductus, but they stabilized or reduced the diameter of the ductus arteriosus and resulted in clinical improvements, thus allowing the subsequent use of indomethacin and successful closure of the ductus arteriosus. Similar effects were not observed when paracetamol was used as a second-line treatment after ibuprofen failure. Some authors reported that failures or recurrences may occur after initial therapy with ibuprofen or paracetamol for the treatment of PDA. Prior treatment with ibuprofen may also negatively influence the response to paracetamol treatment [26–29].

One important consideration is the period of diuresis reduction to establish the risks and benefits of the respective treatments. In the present study, this alteration which indicates acute renal dysfunction, manifested within a time period that was close to ductus arteriosus closure, which may not represent a risk for neonates. Another important consideration is the benefit of indomethacin treatment with regard to hemodynamic consequences (e.g., left-right shunt, sequelae of hypoperfusion-renal ischemia, intestinal infarction, periventricular leukomalacia, congestion, and pulmonary edema), which may occur in the absence of treatment and cause a greater risk to preterm infants with PDA [1,2].

The present results should be interpreted with caution because they derive from a non-controlled study with a limited number of subjects. Furthermore, the data were collected from only one Neonatal Intensive Care Unit. However, the findings may be important for preterm neonates with severe CHRs with manifestations that contraindicate the use of indomethacin, especially in countries where these drugs are available only in oral dosage form.

In summary, this case series found greater efficacy of orally administered indomethacin for the treatment of PDA in premature neonates with severe CHRs in a Neonatal Intensive Care Unit. Oral treatment with paracetamol or ibuprofen in premature neonates with severe CHRs and contraindications for indomethacin was ineffective for PDA closure. However, results in clinical improvements of this neonates allowed the subsequent use of indomethacin and successful closure of the ductus arteriosus. This case series demonstrated that indomethacin treatment resulted in a greater reduction of diuresis compared with the other drugs. Nevertheless, should be considered the benefit

of indomethacin with regard to hemodynamic consequences which may occur in the absence of treatment, and cause a greater risk to preterm neonates with PDA.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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