



Comparison of Oral Paracetamol with Oral Ibuprofen in Closing Patent Ductus Arteriosus in Premature Neonates: A Randomized Controlled Trial

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Abstract

Objectives: Patent ductus arteriosus (PDA) is one of the most common congenital heart diseases. Physiologically, the closure of the ductus arteriosus occurs within 48-72 hours after birth in healthy term neonates. This study aimed to compare oral paracetamol and oral ibuprofen in the closure of PDA in preterm neonates.

Materials and Methods: This study is a single-blind randomized clinical trial. A total of 90 preterm neonates with a gestational age of less than 32 weeks were divided into two groups of oral ibuprofen and oral paracetamol. Oral ibuprofen was administered at a dose of 10 mg/kg on the first day and 5 mg/kg on the second and the third days. Oral paracetamol was administered at a dose of 10 mg/kg every 6 hours for 3 consecutive days. The primary outcome measure was the closure of the ductus arteriosus. The secondary outcome measure was the assessment of any type of complications following the administration of oral paracetamol.

Results: The DA closure rate was 82.2% in the oral paracetamol group and it was 91.41% in the oral ibuprofen group $P < 0.65$, (odds ratio [OR] = 2.22, 95% CI = 0.62-7.97). We did not see any unwanted complication during treatment with oral paracetamol.

Conclusions: The present study showed that oral paracetamol is effective in the closure of PDA. On the other hand, it does not cause any unwanted side effects on the patient.

Keywords: Acetaminophen, Ibuprofen, Patent ductus arteriosus, Premature infant

Introduction

Ductus arteriosus (DA) closure is a sensitive part of the circulatory adaptation after birth. Patency of this duct is one of the most common congenital heart diseases (1). The incidence of Patent ductus arteriosus (PDA) in term neonates is 1 in 2000 birth. PDA in preterm neonates is related to gestational age and weight. Reports show that DA remains open in 70% of very low birth weight neonates, comparing to 40% of infants weighing less than 2,000 g at birth (2,3). The DA constricts after birth in response to reduced PGE2 level and elevated levels of oxygen. Preterm infants often have hypoxic events, and serum PGE2 level is higher in them than in term neonates. These two factors, hypoxia and increased PGE2, cause DA to remain open after birth.

PDA causes left-to-right shunt with an increase in blood flow to the pulmonary artery that leads to congestion and pulmonary edema, so it disturbs oxygen exchange, and the neonate requires more support via the ventilator. On the other hand, open DA increases the incidence of intraventricular hemorrhage (IVH) by the 'steal phenomenon' (4). Diastolic flow through the DA leads

to splanchnic hypoperfusion followed by an increased risk of necrotizing enterocolitis (NEC) (5). For a long time, cyclooxygenase inhibitors, intravenous or oral ibuprofen, and intravenous indomethacin are the main therapy to close the PDA, but treatment with ibuprofen and indomethacin has limitations (6). Contraindications for these medications include thrombocytopenia less than 60000, active bleeding, kidney failure, NEC, IVH, gastrointestinal intolerance, and hyperbilirubinemia (7). Therefore, it is necessary to find alternative therapies for PDA treatment in preterm neonates. After the introduction of the accidentally known effect of paracetamol to neonatologists (8), nowadays, the literature supports the use of paracetamol for closing the PDA in preterm neonates, one of the most important of which is a Cochrane review (9). Intravenous paracetamol has shown good efficacy in closing the PDA, particularly when nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated or are unable to close PDA (10). Intravenous paracetamol (Apotel) was available in our ward, which contained benzyl alcohol. Benzyl alcohol can increase the risk of seizure and developmental delay

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Key Messages

What is the current knowledge?

- ▶ Current studies use mostly intravenous Paracetamol, and most studies show its superiority to Ibuprofen.
- ▶ No complication was reported due to the administration of oral acetaminophen.
- ▶ Some current studies did not mention excluding benzyl alcohol as a preservative in intravenous Paracetamol

What is new here?

- ▶ Oral Paracetamol is effective in closing PDA, but it is not superior to oral Ibuprofen.
- ▶ In cases where intravenous Paracetamol contains benzyl alcohol, oral Paracetamol is as effective as oral Ibuprofen.
- ▶ Oral Paracetamol is better not to be used in neonates under a ventilator.
- ▶ Response to PDA closure is different in neonates less than 30 weeks of GA.

in neonates (11). Benzoic acid is a metabolite of benzyl alcohol that finally is converted to hippuric acid, but due to the immaturity of detoxification in the liver and kidney, benzoic acid accumulates in the preterm neonate's body (12). Therefore, drugs containing benzyl alcohol are not FDA-approved for preterm neonates (13). In conditions that NSAIDs are contraindicated, we need an alternative oral drug; therefore, we decided to compare the efficacy of oral paracetamol and oral ibuprofen.

Materials and Methods

Study Design

The study is a non-inferiority, parallel-arm, single-blinded randomized trial.

Patients

The present study is a randomized clinical trial that was performed in AL Zahra Teaching Hospital of Tabriz University of Medical Sciences, from November 2018 to November 2019. Al Zahra hospital is a tertiary referral maternity hospital with 50 neonatal intensive care unit (NICU) beds. We performed the clinical trial in compliance with the protocol. We enrolled 90 neonates with a gestational age of 32 weeks or less in the study.

Eligibility Criteria

Including Criteria

All neonates with a gestational age ≤ 32 weeks, birth weight ≤ 1500 g, LA: AO ratio > 1.5 , ductal diameter > 1.5 mm (14), hyperdynamic precordium, and bounding pulses were included in the study.

Excluding Criteria

Neonates with following criteria were excluded: renal failure (urine output < 1 mL/kg/h), serum creatinine above 1.8 mg/dL (15), IVH > 2 , active bleeding, thrombocytopenia less than 50 000 (16), gastrointestinal intolerance (increased gastric residual volumes $> 50\%$, abdominal distension,

emesis, or both) (17), gastrointestinal obstruction, coagulation disorders (prolonged prothrombin time or partial thromboplastin time), bilirubin in the moderate risk zone (18), PDA-dependent congenital heart disease, pulmonary arterial hypertension with the right-to-left shunt, proven or suspected NEC, sepsis, and intubation.

Enrollment Process

Consent

The nature of the disease was explained to parents by figures until they understood. After an explanation of the study to the parents, a formal written informed consent was obtained from the parents. After this process, the neonate was enrolled in the study. The parents were free to withdraw their neonates from the study whenever they wished.

Echocardiography

All neonates have been screened three days after birth with echocardiography (SONOSITE M-TURBO USA) with a 4-8 MHz probe. We started the treatment in neonates with large PDA (increased left atrial to aortic root diameter ratio (LA: AO) > 1.5 , large ductal diameter > 1.5 mm), and then echocardiography was repeated one day after the first course of drug therapy. We defined success in treatment by complete closure of DA or small non-hemodynamically DA confirmed by echocardiography.

Allocation Process

Randomization and Blinding

The study is a single-blinded randomized trial. We randomly allocated preterm neonates to two groups of oral paracetamol or oral ibuprofen by Randlist software. Considering that drug containers of paracetamol and ibuprofen were not similar to each other and that blinding the nurses to these containers was not ethical, they were not blinded. However, physicians, patients, and their parents were blind to the containers. Additionally, the statistical analyst was not aware of the patient groups; therefore, only nurses were aware of the contents of the drugs.

Drug Administration

Oral ibuprofen (ibuprofen suspension 100 mg/5 mL, Alborz Darou, Iran) was administered at a dose of 10 mg/kg on the first day and 5 mg/kg on the second and third days (19). Oral paracetamol (Paracetamol syrup 120 mg/5 mL, Razak, Iran) was administered at a dose of 10 mg/kg every 6 hours for 3 days (20). ALT (IU/mL) and AST (IU/mL) levels were checked based on the 50th percentile of GA after the final course of therapy (21). Body temperature was measured every 6 hours if the temperature was below 36.5°C, the set point of the heater was increased by 1°C (22). The primary outcome measure was the closure of the PDA. The secondary outcome measure was the comparison of complications following

the administration of oral paracetamol and oral ibuprofen.

Sample Size

The sample size was determined based on a type I error rate of 0.1, a type II error rate of 0.2, a power of 0.7 for paracetamol group, and a power of 0.9 for the ibuprofen group. Under these conditions, the total population included 90 neonates that were divided into two groups, each group with 45 neonates.

Statistical Analysis

We analyzed the data by R software version 3.6.1. We implemented descriptive statistics (frequency and percentage) and mean ± SD. For contingency tables with cell counts more than 5, chi-square test was used, and for contingency tables with cell counts less than 5, Fisher’s exact test was used to compare qualitative data. In order to compare the quantitative data, we used Wilcoxon. $P < 0.05$ was considered statistically significant.

Results

Our primary outcome measure was PDA closure. We considered the closure of the duct as the success of the treatment, and the success rate was 82.3% in the oral paracetamol group vs. 91.1% in the oral ibuprofen group, which was not statistically different $P < 0.65$, (odds ratio [OR] = 2.22, 95% CI = 0.62-7.97) (Figure 1). Eleven preterm neonates that required intubation were excluded from the study. The most common cause of death in

both groups was sepsis. The mean age of starting oral ibuprofen was 4 days, and for the oral paracetamol group, it was 5 days. In 4 cases, AST level was more than 50th percentile and less than 90th percentile for GA in the oral paracetamol group, although none of the patients had any signs of hepatotoxicity. We did not detect hypothermia during treatment with oral paracetamol.

Based on the Kolmogorov-Smirnov test, the normality assumption does not hold for birth weight and gestational age (weeks) (Table 1). For non-parametric data, Wilcoxon test was used. The difference between the two groups in terms of birth weight and gestational age was not significant ($P = 0.14$, $P = 0.84$), respectively. Regarding steroid and Apgar score (1 minute), based on the chi-square test, there was no significant difference between the two groups. Considering the 5-minute Apgar score, because the cell counts were less than 5, Fisher’s exact test was used (Table 2). Based on this test, there was no significant difference between the 2 groups. For NEC, gastrointestinal bleeding, renal failure, pulmonary bleeding, sepsis, and death ratio, the cell counts were less than five so we used Fisher exact test (Table 3).

Discussion

Based on our NICU guidelines, all preterm neonates are managed with nasal CPAP from the delivery room, and it continues until the neonate needs no more ventilatory support. Intubating preterm neonates is based on the

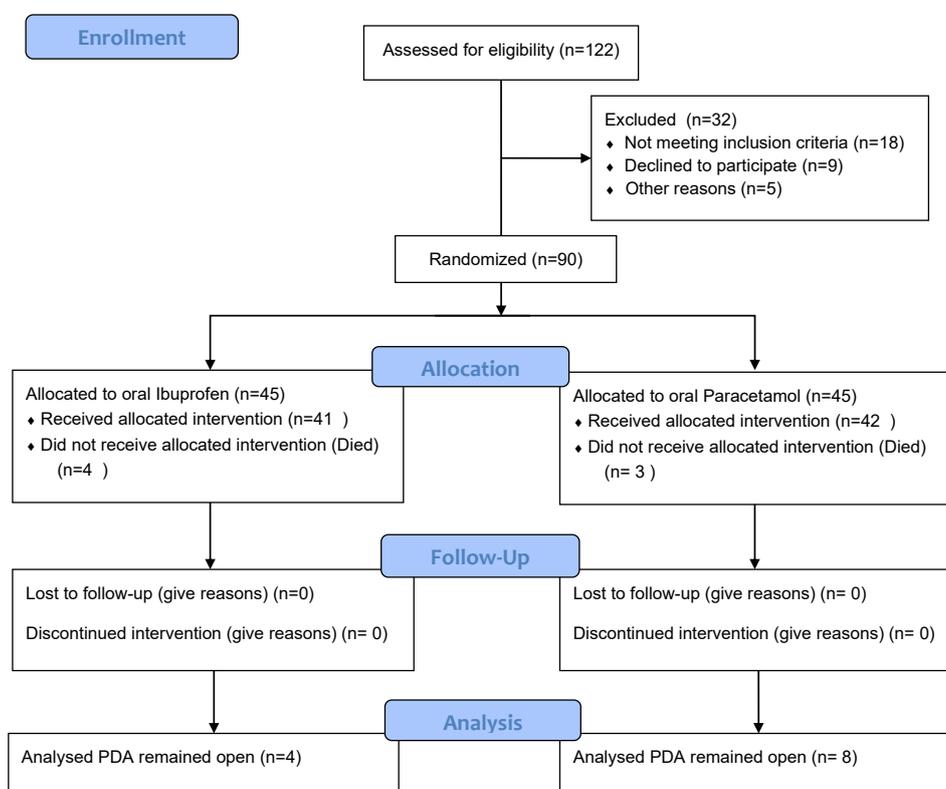


Figure 1. Consort Flow Diagram of the Enrolled Neonates.

Table 1. Demographic Information: Quantitative Variables

Variable	Paracetamol (n = 45)	Ibuprofen (n = 45)	P Value
Median birth weight (g), IQR	1000 (250)	950 (210)	0.14
Median gestational age (wk), IQR	29 (2)	29 (2)	0.84

IQR, interquartile range.

Table 2. Demographic Information: Qualitative Variables

Variable	Paracetamol (n=45)	Ibuprofen (n=45)	P Value
Sex (male)	20	17	0.67
Cesarean delivery	8 (%17.8)	10 (%26.7)	0.06
Steroid	22	21	0.42
Apgar score (1 min)			
≤3	13	13	0.97
4-6	21	18	
>6	11	14	
Apgar score (5 min)			
≤3	4	3	0.99
4-6	9	8	
>6	32	24	

Table 3. Morbidity Information

Variable	Paracetamol (n = 45)	Ibuprofen (n = 45)	P Value
IVH (grade >2)	8	5	0.37
ROP	4	4	-
NEC (>stage 2)	3	4	0.50
GI bleeding	2	3	0.5
Renal failure	1	2	0.5
Pulmonary bleeding	3	3	0.66
Sepsis	7	6	0.76
Death	3	4	0.70
Hospital stays	26.35 ± 2.23	28.75 ± 10.26	0.432

IVH, Intraventricular hemorrhage; GI, Gastrointestinal bleeding

European RDS guidelines (2019). In our experience, most of the preterm neonates, especially ELBWs who require intubation, usually have gastric intolerance, that is why there is a tendency towards intravenous drugs. In our study, we did not use oral paracetamol in intubated neonates, and all the preterm neonates were under nasal CPAP. Given that we did not have intravenous indomethacin for prophylactic closure of PDA and that intravenous Ibuprofen was very expensive due to our condition, and on the other hand, we had some limitations in using NSAIDs during medical conditions mentioned above, we needed a substitute for closing the duct. We have recently learned a lot about the effect of intravenous paracetamol on DA (23). The only available drug in our market was intravenous paracetamol (Apotel) which contained benzyl alcohol as a preservative that is hazardous to the preterm neonate. Meanwhile, oral paracetamol is cost-effective. Our study showed that paracetamol was not superior to ibuprofen. PDA closure rate was higher in the ibuprofen group than in the paracetamol group, but this was not

statistically significant. Lu et al showed that oral ibuprofen was more potent than oral paracetamol in PDA closure (24). A study conducted by Pharande et al showed that oral paracetamol was accompanied by complete closure following intravenous ibuprofen failure, but we cannot ignore the additive effect of ibuprofen and paracetamol (20). Babaei et al reported that PDA was closed in 75% of patients following paracetamol administration, but their study did not have a control group (25). The results of a study conducted by Balachander showed that there was no significant difference between paracetamol and ibuprofen in closing PDA (26). GA and birth weight chosen in their study were in a vast range (< 34 weeks). Prostaglandin-H2 synthetase (PGHS) is an enzyme that comprises of two sites, a cyclo-oxygenase (COX) site and a peroxidase (POX) site. The COX site converts arachidonic acid to PGG2, then POX site of the enzyme forms PGH2. PGH2 is subsequently converted to PGF2α, PGE2, and PGI2. NSAIDs inhibit COX part and paracetamol inhibits the POX part. PGE2 is a prostaglandin derivative and biosynthetic form of arachidonic acid which works as a powerful vasodilator, with biological effects on smooth muscles. The decrease of PGE2 level, which has a critical role in regulating the anatomical structure and vascular tone of the DA, results from increased metabolism in the lungs by active transport pathway involving 15-hydroxyprostaglandin dehydrogenase (HPGD) or by inhibition of the enzyme cyclooxygenase. PGE2 level decreases after 30 weeks of GA and birth weight of more than 1000 g, so in most cases, PDA closure occurs spontaneously (27). The design of the study by AL-lawama et al was similar to that of our study, but PDA closure rate in their study was lower than ours (69% versus 82%) (28). The main difference between our study and other studies is that we excluded neonates requiring intubation due to gastric intolerance in unstable preterm neonates and hypoxic events during ventilation. Our secondary outcome measure was the frequency of morbidities. IVH was more frequent in the paracetamol group than in the ibuprofen group, but this was not statistically significant. AST levels in four cases were in the upper limit range without hepatotoxicity. N-acetyl-p-benzoquinone imine (NAPQI) is a byproduct which is generated during the metabolism of Paracetamol (29). NAPQI reduces the antioxidant activity of the liver by decreasing glutathione level, thereby leading to cell damage in the liver (30). New and more sensitive biomarkers for liver damage are identified such as plasma glutamate dehydrogenase and long-chain acylcarnitines (31), which were not implemented in this

study due to the limitations. Glucuronidase maturation improves paracetamol metabolism and avoids the production of NAPQI. Moreover, its activity improves with higher weight and GA (32). The other secondary outcomes were similar in the two groups.

Limitation of the Study

Our study limitation was that we could not measure the serum paracetamol level after the administration. By controlling serum concentrations of paracetamol, we might better understand drug absorption through the gut in preterm neonates.

In order to improve the study design, it may be better to categorize the groups based on birth weight <1000 g or GA <30 weeks as the PGE1 levels in these groups are higher. Measuring urine PGE1 before and after the therapy and comparing the closure of PDA are recommended. We used low dose paracetamol (10 mg/kg) every 6 hours, and we did not repeat the therapy despite failure. Studying with higher doses with the control of liver function is recommended. Measuring long-chain acylcarnitine level may be a better option for diagnosing liver failure than aspartate transaminase and alanine aminotransferase.

Conclusions

Based on the results of our study, oral paracetamol is as effective as oral ibuprofen in the closure of PDA in premature neonates. It is cost-effective and easy to use. During treatment with oral paracetamol, we saw no complications such as hepatotoxicity or hypothermia. Oral paracetamol can be a safe replacement for oral ibuprofen in cases where NSAIDs is contraindicated, but a better research design is required to ensure its effectiveness as a first-line treatment.

Authors' Contribution

KM and MS designed the study. ZN and RP performed the study. AS and RKH designed the method.

Conflict of Interests

The authors declare that they have no conflict of interests.

Ethical Issues

The Ethics Committee of Tabriz University of Medical Science approved the research on July 26, 2014 (No. 9346). This study was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20171227038102N1; <https://www.irct.ir/trial/30912>).

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