The Comparison between Acetaminophen and Ibuprofen Effectiveness for Ductus Arterious Closure Therapy in Premature Infants

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Abstract

The patent ductus arteriosus can cause heart failure, metabolic acidosis, necrotizing enterocolitis (NEC), and pulmonary edema/bleeding. Ibuprofen has been proven to have similar efficacy in closing ductus arteriosus but has side effects, such as kidney and intracranial bleeding. There is a report in a case series, the closure of the ductus arteriosus occurred in five premature babies given oral acetaminophen.

This study aims to identify the effectiveness of acetaminophen compared with ibuprofen for ductus arteries closure in premature infants.

This study employed a quasi-experimental study design. This study involved two groups, i.e., the first group was given oral ibuprofen (control), and the second group was given oral acetaminophen. The number of subjects amounted to 11 infants in each group. The ductus arteriosus examination in each group was in the form of echocardiographic examination with two dimensional and Doppler imaging before and after the treatment. The data obtained were analyzed using the Fisher exact test, t-test, and chi-square.

After the therapy for one and two series had performed, the DA closure in infants of the ibuprofen group reached more than those in the acetaminophen group. The statistical analysis suggested that DA closure had the results that were insignificantly different (p-value of 1.000). Acetaminophen has similar effectiveness as ibuprofen in closing the ductus arteriosus in premature infants.

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Introduction

Ductus arteriosus (DA) is a blood vessel that connects the proximal descending aorta and pulmonary artery. The essential structures in the fetus normally close after birth [1]. The open ductus causes an increase of pulmonary blood flow and a decrease of blood flow to the intestinal organs, skin, muscles, and kidneys, resulting in heart failure, metabolic acidosis, necrotizing enterocolitis (NEC), and pulmonary edema/bleeding [2]. Those conditions can occur if the open ductus arteriosus is hemodynamically significant, particularly if the diameter is more than 1.5 mm [3].

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Indomethacin and ibuprofen have been proven to have similar efficacy in closing ductus arteriosus. Both therapeutic modalities work through the inhibition of the cyclooxygenase enzyme, so prostaglandin synthesis is inhibited [4]. Indomethacin has side effects on the kidneys, which is a higher increase of serum creatinine when compared to ibuprofen and lower urine output in 19% of patients [5]. Meanwhile, the side effects of ibuprofen include gastric bleeding, amounting to 10% patients, and intracranial amounting to 20% patients, especially in thrombocytopenia patients [6].

In a case series report, the closure of the ductus arteriosus occurs in 5 premature infants given oral acetaminophen. Two of five ductus arteriosus cases can close after they fail to close on the administration of two oral ibuprofen series. In that case, three of five infants develop thrombocytopenia, and one infant develops hyperbilirubinemia. There is no reported gastric bleeding in thrombocytopenic patients[7].

Meanwhile, the research reveals that the incidence of gastric bleeding was much smaller by using acetaminophen than ibuprofen [8]. In Indonesia, the research data on the use of oral acetaminophen as medical therapy to close ductus arteriosus in premature infants is still limited [9]. This study focuses on the oral acetaminophen effectiveness compared to oral ibuprofen for the ductus arteries closure in premature infants.

Materials and methods

This study employed a quasi-experimental study design. The study samples were all premature infants whose DA were still open and met the criteria, i.e., premature infant patients aged of less than 21 days, gestational age 26-37 weeks with open ductus arteriosus, ductus diameter of greater than 1.5 mm, platelet count of greater than 50,000/mm^3, and patients whose parents had signed informed consent. The other related data was also collected, such as sex, birth weight, chronological age (days), the presence or absence of heart failure, and the presence of respiratory distress syndrome. In this study, two groups were involved, i.e., the first group was given ibuprofen (control), and the second group was given acetaminophen. The study involved 11 subjects in each group.

The echocardiographic examination had been recognized as one of the examination methods of cardiovascular activity and abnormalities[10–12]. The ductus arteriosus examination in each group was in the form of echocardiographic examination with two dimensional and Doppler imaging before and after the treatment. The patients in treatment and control groups were administered drugs orally by nurses in the hospital. The administration of acetaminophen at a dose of 15 mg/kg/time was performed four times per day for three days. The administration of ibuprofen was performed at a dose of 10mg/kg on the first day, 5mg/kg on the second and third days. Echocardiographic evaluation was conducted one day after completing one series. In case that the constriction of DA diameter did not occur after one series of acetaminophen or ibuprofen, the next series would continue (maximum for two series). After completing the second series, echocardiography evaluation was conducted one day after the series completed. The data obtained were analyzed using the Fisher exact test, t-test, and chi-square.

Results

Baseline characteristics before the study in both groups of homogeneous subjects, both sex, gestational age, birth weight, chronological age, DA diameter, platelet count, as well as those suffering from heart failure and respiratory distress (RDS) syndrome with a significance of p-value of greater than 0.05 so that there is no difference meaningful between the two groups. It should be noted that platelet counts in both groups were above 50,000/mm^3 so that research was secure to carry out. The characteristics of the two groups' samples examined can be seen in Table 1.

Characteristics	Acetaminophen (n)	Ibuprofen (n) (control)	*p*
Gender			1.000*
Male	4	5	
Female	7	6	
Gestational age (weeks)	33.7 ± 1.7	34.9 ± 1.4	0.098**
<28	-	-	
28-<32	1	1	
32-<34	5	2	
34-37	5	8	
Birth weight (g) (mean ± SD)	1,722.7 ± 170.8	1,904.5 ± 315.0	0.108**
1,000 - <1,500g	-	1	
1,500 - <2,500g	11	10	
Chronological age (days) (mean ± SD)	7.7 ± 5.7	8.00 ± 6.1	0.915**
Ductus arteriosus diameter (mm)	2.6±0.9	3.1±1.1	0.236**
Heart failure	4	4	1.000*
Respiratory distress syndrome	2	2	1,000*
Platelet count (/mm^3) (mean ± SD)	249,000.0±134,902.1	280,636.3±151,026.6	0.610**

Table 1. The characteristics of subjects given acetaminophen and ibuprofen.
* Fisher exact test; ** Independent t-test

	One series		
	Acetaminophen	Ibuprofen (control)	*p*
Ductus arteriosus reduction (mm) (mean±SD)	-1.5±1.2	-1.9±1.5	0.503**

Table 2. The size reduction comparison of the ductus arteriosus after one series administration of acetaminophen and ibuprofen.
** Independent t-test

1st Series	2nd Series					
	Acetaminophen	Ibuprofen	*p*	Acetaminophen	Ibuprofen	*p*
Closed	4	6	0.670**	8	9	1,000*
Remained open	7	5		3	2	

Table 3. The comparison of ductal arteriosus closure between acetaminophen and ibuprofen.
*Fisher exact test, ***Chi-square test

The mean reduction in DA size after ibuprofen one series of therapy (1.9±1.5 mm) reached greater than after one series of

acetaminophen therapy (1.5±1.2 mm). However, the two groups did not differ statistically (p-value of 0.503). After the therapy for one and two series had performed, the DA closure in infants of the ibuprofen group reached more than those in the acetaminophen group. However, if the statistical analysis was performed, the result was insignificant (p-value of 1.000).

Discussion

The change of DA size could be determined by comparing the ductus diameter before and after the therapy. The change of DA size after administration of one therapy series in both groups was insignificant (p-value of 0.503). It indicated that acetaminophen and ibuprofen had similar effectiveness. In a similar way, ibuprofen inhibited prostaglandin production through the COX enzyme[4,13,14] inhibition, and the acetaminophen did likewise[15].

The administration of both acetaminophen and ibuprofen therapy began since DA was identified still open. Several study subjects were under one week old, consisting of 3 subjects in the acetaminophen group, and two subjects in the ibuprofen group were aged less than four days. Gestational age was one of the determining factors in DA closure. For healthy premature infants and 90% premature infants with RDS and with the gestational age of greater than or equal to 30 weeks, the ductus arteriosus would close on the fourth day. Meanwhile, for the premature infants with a gestational age of less than 30 weeks and suffering from RDS, 65% of the ductus remained open after the fourth day[16].

Birth weight was a determining factor for the ductus arteriosus closure[17]. The infants with a birth weight of more than 800g had DA closure rate reached 85.5%, which differed significantly from those whose birth weight was lesser, amounting to 68.3%[17]. Infants with birth weight above 1,500g, the closure rate reached 80% [8]. A thicker DA wall caused that results.

The effective age to begin the therapy was younger than a week[18]. The infants who were younger than 40 hours old would result in a significant difference in the DA closure rate when given indomethacin, compared to those older than 40 hours or a p-value of less than 0.05 [17]. Although the study subjects in the ibuprofen group had a larger mean diameter of DA, the result was not significantly different (p-value of 0.236). Despite the possibility that DA closed spontaneously [19], both ibuprofen and acetaminophen therapy were still given because DA was hemodynamically significant.

Moreover, ductus arteriosus could cause heart failure [20]. The eight subjects with heart failure (4 in each group) exposed hemodynamically significant DA consequences. Even though the entire study population had hemodynamically significant DA measurements, not all of them had signs of heart failure. During the fetus stage, pulmonary artery pressure was high, while in the neonatal period, the pressure would decrease slowly. This high pressure caused the symptoms of heart failure not experienced by all premature infants [21,22].

The safety of study subjects was guaranteed because only infants with platelet counts above 50,000/mm^3 were included in the study. The platelet count with the aforestated amount was required before starting therapy with COX inhibitors [13].

DA constriction initiated the remodeling and the ductus closed anatomically at the end. Both acetaminophen and ibuprofen decreased prostaglandin production so that the vasa vasorum in the DA wall constricted (Narayanan-Sankar, 2003; Hinz, 2008; Hinz, 2012). That condition would trigger a remodeling cascade, which was hypoxia-inducible.

The DA closure rate in this study was nearly similar to the previous study results, which signified that the DA closure rate by using acetaminophen and ibuprofen reached 81.2% and 78.8%, respectively[8]. The results corroborated that acetaminophen was comparable to ibuprofen as DA closure therapy in premature infants. Acetaminophen became an alternative to ibuprofen when ibuprofen was a contraindication, specifically if the thrombocytopenia below 50,000/mm^3[4–6].

Acetaminophen had the advantage that COX enzyme inhibitors do not own it, i.e., inhibits peroxidase reactions. That advantage made acetaminophen more effective than NSAIDs and selective COX-2 inhibitors since they did not need to compete with arachidonic acid to inhibit prostaglandin production[23].

Acetaminophen and ibuprofen bioavailability measurements were not performed in this study. Premature infants with a greater but unstable DA, such as the infants with birth weight less than 1,500g or infants with a mechanical

breathing machine, could be included in this study due to the unavailability of portable echocardiography.

Conclusions

Oral Acetaminophen can be used as an alternative drug to ibuprofen to close the ductus arteriosus (DA). Oral acetaminophen has similar effectiveness with oral ibuprofen to close the ductus arteriosus in premature infants.

Declaration of Interest

The authors report no conflict of interest.

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