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Comparative Study of the Efficacy of Oral and Intravenous Acetaminophen in Closure of Patent Ductus Arteriosus of Preterm Neonates

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Abstract

Background and Aim: Patent ductus arteriosus (PDA) is a condition in premature infants that can cause dangerous complications such as renal dysfunction, intracerebral hemorrhage, necrotizing enterocolitis, and pulmonary dysplasia. This study was conducted to compare the efficacy of oral and intravenous acetaminophen in PDA improvement in preterm infants.

Methods: This randomized clinical trial study was performed on 100 children. The patients were randomly divided into two groups. Group A received intravenous acetaminophen and group B was treated with oral acetaminophen for three consecutive days. Echocardiography was performed before and 3 and 6 days after the intervention.

Results: Before the intervention, the prevalence of a small PDA was 72% and 76% and the prevalence of a large PDA was 28% and 24%, in group A and B, respectively. The second echocardiography showed a significant PDA improvement in both groups ($p<0.001$). The third echocardiography showed that all patients (100%) in the oral acetaminophen were treated while only three patients (6%) in the IV acetaminophen group had a large PDA. Intravenous injection of acetaminophen significantly decreased LA/AO (Left Atrial/Aortic root diameter) ratio from 1.46 to 1.27 ($p=0.043$). Similarly, oral acetaminophen declined LA/AO ratio from 2.0 to 1.30 ($p=0.018$). At the end of the second course of treatment, the prevalence of complete cure was 100% and 94% in groups A and B, respectively.

Conclusion: Oral administration of acetaminophen improved PDA treatment without any adverse effects. Therefore, IV injection of acetaminophen can be replaced with oral acetaminophen for management of PDA in preterm infants.

Keywords: Patent Ductus Arteriosus; Acetaminophen; Preterm Neonates; Echocardiography.

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Introduction

Ductus Arteriosus (DA) is a vascular connection between pulmonary artery (PA) and aorta that is regarded as one of the essential shunts of prenatal life circulation (1). Patent Ductus Arteriosus (PDA) is a physiologic shunt in healthy full-term and preterm neonates that commonly manifests itself during the first three days of life.

The severity of the problem depends on the degree of shunt opening. Failure in spontaneous DA closure can lead to dangerous clinical consequences. This situation may be associated with numerous pulmonary complications like respiratory failure, pulmonary edema, reduced alveolar growth, and decreased pulmonary

compliance (1, 2). In severe cases, it can lead to chronic lung disease (CLD), systemic hypo-perfusion causing renal failure, metabolic acidosis, intracranial hemorrhage and necrotizing enterocolitis (NEC), each of which can be a direct cause of death (3). In fact, PDA increases mortality in the preterm infants by 4-8 folds (4). Moreover, untreated PDA can lead to decreased cerebral perfusion and even neural damage (5). The incidence of PDA in full-term neonates is 57 in 100,000 live births while it occurs in approximately one-third of the premature infants with birth weight 501-1500 grams (1). Moreover, about 55% of the neonates with birth weight less than 1000 grams may develop a symptomatic PDA (6, 7). There is a direct relationship between gestational age and spontaneous PDA closure. Functional closure of DA occurs within 24 hours in almost 50% of full-term neonates, within 48 hours in 90%, and within 72 hours after birth in all term infants. Duct closure occurs by day four of life in healthy preterm neonates with gestational age more than 30 weeks, it occurs between days two to six of life in only 34% of extremely low birth weight infants (ELBW) (8).

There are still unanswered questions regarding treatment of PDA. At the present time, the most common treatment options for PDA in preterm infants include surgical and pharmacologic closure using drugs such as cyclo-oxygenase inhibitors (9). Hemodynamically stable PDA cases usually respond to medical therapy with non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen (9-11). This can be associated with several side effects, including nephrotoxicity and gastrointestinal bleeding. Surgery is an option for treatment of cases with failed medical management. However, duct ligation is associated with some complications like pneumothorax, chylothorax, and infection. Vocal cord paralysis, feeding difficulties, and respiratory complications are other common side effects of surgical closure of PDA (12). Additionally, surgical closure of PDA may increase the risk of bronchopulmonary dysplasia (BPD) (13). BPD is characterized by impaired pulmonary alveolar and vascular growth along with a prolonged need for mechanical ventilation (13). This condition potentially deteriorates pulmonary mechanics. Besides, surgical closure of PDA during the neonatal period is markedly associated with neurodevelopment disorder, chronic lung disease, and retinopathy of prematurity (ROP) (14). On the other hand, many premature infants who undergo surgical closure for PDA may not have favorable long-term cardiopulmonary outcomes (14).

Nowadays, researchers prefer to apply less invasive methods for treatment of PDA in neonates to enhance alveolar development and pulmonary function (15). Recent studies have shown that intravenous (IV) or oral Paracetamol (Acetaminophen) may be effective for management of PDA in preterm infants (16). A positive point is that it is less nephrotoxic than Ibuprofen. However, it is not studied widely in prospective clinical trials. There is no consensus among neonatologists regarding the management of PDA (2). Despite the high prevalence of PDA in preterm infants, the idea to use pharmacological interventions to enhance PDA closure is still controversial. The objective of the current study was to investigate effectiveness of oral and intravenous Acetaminophen for management of PDA in preterm infants.

Methods

Patient's selection

This clinical trial study was conducted on preterm neonates with PDA who were admitted to the neonatal ward of Aliasghar Children's Hospital, Tehran, Iran between 2018 and 2019. The study was approved by the Ethics Committee of Iran University of Medical Sciences and registered in the Iranian Registry of Clinical Trials (IRCT20190505043478N1). Before patient selection, a checklist was prepared to record demographic characteristics, basic clinical data, drug history, duration of ICU stay, and inotrope administration at the time of hospitalization. Informed consent was obtained from all parents before the study. Children with a history of endocrine or cardiovascular disorder, congenital anomalies, and congenital heart or renal disease were excluded from the study. The patients who had renal dysfunction on admission or used any type of antioxidant supplementation at the time of study were also excluded.

The neonates who had echocardiographic proven pulmonary hypertension, intraventricular hemorrhage grade 3-4, co-existing life-threatening infections, congenital anomalies or congenital heart disease were excluded from the study. In addition, the neonates who were on treatment with Paracetamol or NSAIDs for any reason were not enrolled. Inclusion criteria were gestational age >26

weeks and < 37 weeks, hospital admission within 24 hours of birth, PDA size > 2mm confirmed by echocardiography within first three days after birth. The sample size was calculated based on the results of a previous study (17). Accordingly, 100 PDA cases were enrolled in the study.

After patient selection based on the inclusion and exclusion criteria, a checklist was prepared to record demographic characteristics and basic clinical data of all cases including sex, weight, gestational age and age at PDA diagnosis were recorded. Clinical signs and symptoms of PDA were examined carefully, including heart murmur, strengthened beat of anterior thorax, locomotive pulse, tachycardia when the neonate was quiet, cardiomegaly or increased pulmonary vascular pattern on chest X-ray, and unexplained oxygen dependency. Echocardiographic results were studied before treatment, three days after treatment, and six days after treatment in those who did not respond to the first course of therapy and required a second course. The echocardiographic diagnostic criterion for PDA was defined as left atrial/aortic root diameter (LA/AO) > 1.4.

Intervention and measurements

The patients were randomly divided into two groups. The first group (n=50) (A) received IV Acetaminophen and the second group (n=50) (B) received oral Acetaminophen. The patients were treated with Acetaminophen at a dose of 15 mg/kg every 6 hours for three consecutive days in both groups. A maximum of two courses was considered. The cases without PDA closure after two courses of therapy with Acetaminophen were considered for treatment with Ibuprofen. Subsequent PDA closure was also investigated clinically by follow-up echocardiography. Echocardiography was repeated upon completion of the three-day treatment course. Frequency of treatment with acetaminophen and response to therapy (complete, incomplete) were studied in each group and compared between the groups. Treatment side effects were monitored carefully. Treatment stopped in case of fever, hypothermia, vomiting, aminotransferase elevation, or hyperbilirubinemia.

Statistical analysis

The quantitative data were analyzed using the descriptive tests and the results are presented as Mean ± SD. The percentage and frequency of each item were compared between the two groups using Crosstabs and Chi-Square tests. Student t-test was applied to compare the mean values the variables between two groups. Paired t-test was used to compare the mean values of quantitative parameters before and after study in each group. In this study, $p< 0.05$ was considered statistically significant. The SPSS software (IBM, version 19) was used for data analysis.

Results

One hundred children with a mean gestational age of 33.35 ± 3.34 weeks were enrolled in the study, of whom 55 (55%) were boys and 45 (45%) were girls. The mean weight and age at diagnosis was 1.99 ± 0.69 kg and 5.13 ± 2.34 days, respectively. Comparison of the basic demographic and clinical characteristics between the two groups is summarized in Table 1. There was no significant difference in the mean gestational age (p=0.24), age at diagnosis (p=0.86), weight (p=0.22), and frequency of sex distribution (p=0.33) between the two groups. Overall, oxygen (O_2) dependence was the most common sign of the PDA in all cases with a prevalence of 86%, while the prevalence of heart murmur and O_2 dependence + murmur was 3% and 11%, respectively.

Table 1. Comparison of demographic and clinical characteristics of patients between treatment groups

Parameters	Acetaminophen		p-value
	Intravenous (A)	Oral (B)	
Gestational age (weeks)	34.0 ± 3.16	32.57 ± 3.5	0.24
Age at diagnosis (days)	5.35 ± 4.32	4.86 ± 4.21	0.86
Weight (kg)	2.13 ± 0.68	1.82 ± 0.70	0.22
Gender			
Boys (%)	26 (52%)	29 (58%)	0.33
Girls (%)	24 (48%)	21 (42%)	
PDA symptoms			
O_2 dependent	42 (84%)	44 (88%)	0.46
Heart murmur	1 (2%)	2 (4%)	
O_2 dependent & heart murmur	7 (14%)	4 (8%)	

There was no significant difference in the prevalence of PDA signs between the two groups

(p=0.46). O_2 dependence was the most common sign of PDA in group A (84%) and B (88%). Comparison of the echocardiographic findings between the two groups is presented in Table 2.

Table 2. Comparison of echocardiographic findings between two groups

Parameters	Acetaminophen		P-Value
	Intravenous (A)	Oral (B)	
First Echo			
Large PDA (%)	36 (72%)	38 (76%)	0.61
Small PDA (%)	14 (28%)	14 (24%)	
Second Echo			
Large PDA (%)	0	0	0.88
Small PDA (%)	12 (24%)	11 (22%)	
No PDA (%)	38 (76%)	39 (78%)	
Third Echo			
Large PDA (%)	3 (6%)	0 (0%)	0.35
Small PDA (%)	0	0	
No PDA (%)	47 (94%)	50 (100%)	

There was no significant difference in echocardiographic findings between the two groups. Before the intervention, the prevalence of small PDA was 72% and 76% and the prevalence of large PDA was 28% and 24% in group A and B, respectively. Second echocardiography (three days after the intervention) revealed a significant PDA improvement in both groups (p<0.001). About 75% of the cases in the both groups did not have a PDA on the second echocardiography. On the third echocardiography, (three days after the second echocardiography) all patients (100%) who received oral acetaminophen were treated and only three patients (6%) in the IV acetaminophen group had a large PDA.

Comparison of the first and second LA/AO ratio between the two groups is demonstrated in Table 3. Intravenous injection of acetaminophen significantly decreased the LA/AO ratio from 1.46 to 1.27 (p=0.043). Similarly, oral administration of acetaminophen reduced the LA/AO ratio from 2.0 to 1.30 (p=0.018). There was no significant difference in the mean value of the first and second LA/AO ratio between oral and IV acetaminophen. No adverse effects were observed in the study groups.

Table 3. Comparison of LA/AO findings between two groups

Parameters	Acetaminophen		p-value
	Intravenous (A)	Oral (B)	
First LA/AO	1.46 ± 0.58	2.0 ± 0.32	0.35
Second LA/AO	1.27 ± 0.35	1.30 ± 0.27	0.84
p-value	0.043	0.018	

In addition, there was no significant difference in the frequency of acetaminophen administration between the two groups (Table 4; p=0.83); 88% of the patients in group A and 86% in group B received one course of treatment and 12% of the patients in group A and 14% in group B received the second course.

Table 4. Comparison of disease treatment progression between two groups

Parameters	Acetaminophen		p-value
	Intravenous (A)	Oral (B)	
Number of therapy			0.83
One course	44 (88%)	43 (86%)	
Two course	6 (12%)	7 (14%)	
PDA status at the end of first course treatment			0.51
Complete	38 (76%)	43 (86%)	
Incomplete	12 (24%)	7 (14%)	
PDA status at the end of second course treatment			0.51
Complete	47 (94%)	50 (100%)	
Incomplete	3 (6%)	0	
PDA time	3.35 ± 0.99	3.46 ± 1.12	0.78

There was no significant difference in the percentage of complete treatment in the first or

second course of treatment between the two groups (Table 4). The prevalence of complete cure in group A and B was 76% and 86% at the end of the first course and 100% and 94% at the end of second course of treatment, respectively (Table 4). There was no significant difference in the mean PDA duration between the two groups (p=0.78). The mean duration of PDA in was 3.35 and 3.46 days group A and B, respectively.

Discussion

This study was conducted to evaluate the efficacy of oral and IV acetaminophen in PDA closure of 100 preterm neonates. There was no significant difference in the mean gestational age, age at diagnosis, weight, sex distribution, and the frequency of PDA signs between the two groups. The frequency of O_2 dependence was about 85% in both groups. The data revealed that both IV and oral acetaminophen equally improved PDA three days after treatments, as 76% of the neonates in the IV group and 78% of the neonates in the oral acetaminophen group did not have a PDA. The third echocardiography showed that neonates in the oral group were completely treated while 94% of the neonates in the IV acetaminophen group were completely cured. We also found that both IV and oral acetaminophen significantly reduced the mean LA/AO ratio. Therefore, the results indicated the high efficacy of oral and IV acetaminophen in improving PDA without any side effects. Since IV administration is a rather invasive method, it could be replaced by oral acetaminophen for the treatment of PDA in premature neonates.

To the best of our knowledge, no study has compared the efficacy of oral and IV acetaminophen for PDA treatment, and most of the studies have compared oral or IV acetaminophen with others drug such as ibuprofen. For example, Dang et al. (18) investigated the efficacy and safety of oral acetaminophen versus oral ibuprofen in 160 premature infants with PDA. They found that both drugs equally improved PDA. Hyperbilirubinemia and gastrointestinal bleeding was slightly lower with acetaminophen compared to ibuprofen. The authors concluded that oral acetaminophen was comparable to oral ibuprofen and could be used as a primary drug for treatment of PDA in preterm infants (18). The results of the above study are consistent with the findings of the present study, as we found that oral acetaminophen improved PDA in premature infants without any side effects. Dani et al. (17) investigated the efficacy and safety of acetaminophen injections and ibuprofen for the treatment of PDA in 110 preterm neonates aged 25-31 weeks. The results showed that oral acetaminophen not only had a higher efficacy than ibuprofen for PDA improvement, but also had fewer side effects. Akbari Asab et al. (19) evaluated the effectiveness of acetaminophen in PDA closure in 32 premature infants and found 75% PDA closure in neonates who received acetaminophen versus 50% in the control group. In a recent study, Mehralizadeh et al. (20) compared the efficacy of oral ibuprofen and IV acetaminophen in PDA closure of 24 preterm infants and found no significant difference in echocardiographic findings between the two groups before and after the interventions. The mean treatment course in infants treated with oral ibuprofen (1 ± 0.625 day) was not significantly different from infants treated with intravenous acetaminophen (1.25 ± 0.62 days). There was no significant difference in the duct closure between the two treatment groups at the end of the first and second treatment periods. The authors concluded that ibuprofen and IV acetaminophen equally improved PDA closure without side effects. Sinha et al. (21) reported that ibuprofen administration (15 mg/kg) was not effective for treatment of PDA in preterm neonates, but oral acetaminophen (15 mg/kg every 8 hours) significantly improved PDA after 48 h without side effects. The results of this study are consistent with the finding of our study. In our study, oral acetaminophen significantly improved PDA and decreased LA/AO ratio in preterm infants without side effects. In another study, Terrin et al. (22) investigated the efficacy of acetaminophen for treatment of PDA in 8 preterm infants (mean birth weight: 724 ± 173 g, mean gestational age: 26 ± 2 weeks). The results showed that ibuprofen and indomethacin administration could not successfully treat PDA and caused several side effects, whereas acetaminophen administration significantly improved PDA without adverse effects. These results are consistent with the findings of the present study. In our study, oral and IV acetaminophen equally improved PDA.

Oncel et al. (23) evaluated the efficacy and safety of oral acetaminophen versus oral ibuprofen for PDA

treatment in 90 preterm with a gestational age of 30 weeks and birth weight of <1250 g. After the first course of treatment, PDA closure was 77.5% and 72.5% in the ibuprofen and acetaminophen group, respectively. The rate of re-opening was slightly higher in the acetaminophen group compared to the ibuprofen group. PDA closure after the second course of treatment was high in both groups. Eventually, only two patients in the acetaminophen group and three patients in the ibuprofen group required surgical closure. The authors concluded that oral acetaminophen could be a good substitute for the treatment of PDA in preterm infants. The results of the present study showed that oral acetaminophen had similar efficacy as IV acetaminophen and could be considered a good substitute for intravenous treatment. Therefore, according to previous accomplished data and the findings of the present study, IV acetaminophen can be replaced by oral administration.

Conclusion

The results of this study showed that oral acetaminophen improved PDA without any adverse effects, especially in the first course of treatment. In the second round of PDA treatment, 100% of premature infants that received oral acetaminophen were treated. Therefore, intravenous injection of acetaminophen can be replaced by oral acetaminophen for management of PDA in preterm infants. However, more studies with larger sample sizes are required to confirm these results.

Conflict of Interest

The author declares no conflicts of interest.

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