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Original Article (Pages: 14077-14083)

The Effects of Acetaminophen Prophylaxis on Patent Ductus Arteriosus Closure in Premature Infants: A Clinical Trial Study

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Abstract

Background

There is little evidence of the efficacy of acetaminophen prophylaxis in preventing PDA in premature infants. Regarding the effects of acetaminophen in these cases and also safety of this drug in preterm infants, as well as the high prevalence of arterial duct in our population, we aimed to determine the preventive effects of this drug on PDA in preterm infants.

Materials and Methods

In this clinical trial, 64 premature infants with gestational age less than 31 weeks were randomly divided into two groups including intervention group receiving acetaminophen prophylaxis (10 mg/kg) every 6 hours for 5 days and the control group did not receive any intervention. After 10 days, both groups were assessed by echocardiography regarding the PDA condition. Serum levels of ALT and AST enzymes were also measured 10 days later and simultaneously with doing echoes.

Results

There was a significant different in the rate of PDA closure across the two intervention and control groups (84.4% versus 50.0%, p = 0.007). After the intervention, open PDA was found in 50% of neonates in control group and 15.6% in intervention group that were treated with ibuprofen and echocardiography was performed again after 1 month. PDA was closed in the remaining 87.5% in the control group and remaining 100% of patients in the intervention group indicating no difference (p = 0.632). The changes in liver enzymes slightly changed after intervention.

Conclusion

Preventive treatment with acetaminophen can effectively lead to PDA closure in premature infants.

Key Words: Acetaminophen, Prophylaxis, Patent arterial duct, Premature infant.

*Please cite this article as: Asadpour N, Choupani R, Kermani M, Salehifard A. The Effects of Acetaminophen Prophylaxis on Patent Ductus Arteriosus Closure in Premature Infants: A Clinical Trial Study. Int J Pediatr 2021; 9(7): 14077-83. DOI: **10.22038/ijp.2020.51940.4150**

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Received date: Nov. 20, 2020; Accepted date: Feb.22, 2021

1- INTRODUCTION

Ductus arteriosus is a natural blood vessel in the heart of the embryo that connects the two main arteries of the heart, the aorta and the pulmonary artery. When the fetus is in the uterus, the lungs of fetus does are completely passive because the fetus provides oxygen directly from the placenta. The presence of ductus arteriosus in the heart of the embryo does not allow blood supply to pulmonary arteries as well as to other organs of the body (1). This duct closes functional in most neonates on the first day of life, but anatomically at the end of the first week. The mechanism of artery duct closure has not yet been well defined; perhaps an increase in arterial oxygenation is the trigger for closure mediated by a complex contraction between autonomic chemical mediators, prostaglandins and ductal muscular tissue (2). Patent ductus arteriosus (PDA) is an abnormal phenomenon, however it remains open in 30-60% of very low birth weight infants (less than 1500 grams).

Spontaneous closure of this duct occurs only in one third of low birth weight infants in the first four days of life and therefore the vast majority of these neonates are candidates for drug and surgical interventions (3). Opening this duct causes the oxygen-rich blood in the aortic artery to be mixed with oxygen-free blood flowing in the pulmonary artery leading finally raised pulmonary blood pressure. Small ductus arteriosus may not cause complications, but large untreated ducts may cause complications such as high blood pressure in the pulmonary arteries, heart failure and heart attack (1). PDA therapies can include monitoring, medication and surgery (1). The surgical closure of the duct is associated with a high mortality rate as well as with neurodevelopmental effects, and thus it remains limited to the time when the arterial duct is significant and drug therapies are prohibited despite the treatment with indomethacin or ibuprofen (2). In premature infants, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or indomethacin, can help close the PDA. NSAIDs inhibit quasi-hormonal chemicals that keep PDAs open (4). Preventive administration of indomethacin has improved the rate of permanent closure of the arterial duct. Also, preventive administration of indomethacin reduces the need for surgical closure of the duct and reduces the intraventricular hemorrhage of the brain, but does not improve the survival rate without developing neurodegenerative defects. Although ibuprofen has similar effects on arterial duct closure, it has fewer side effects (5). There are some reports that acetaminophen can help to close arterial duct. This effect has been mostly seen in pregnant animal models. Recently, studies have also been conducted to investigate the use of acetaminophen as a therapeutic method for PDA closure (1, 7-11). However, there is little evidence of the efficacy of acetaminophen prophylaxis in preventing PDA in premature infants. Regarding the effects of acetaminophen in these cases and safety of this drug in preterm infants, as well as the high prevalence of arterial duct in our population, we aimed to determine the preventive effects of this drug on PDA in preterm infants and, if proven, to improve the health of preterm infants.

2- MATERIALS AND METHODS

2-1. Study design and population

In this double-blind clinical trial, 64 premature infants with gestational age less than 31 weeks who were hospitalized in Hajar Hospital from Jul to Dec 2019. were included in this study using a simple convenient sample method according to a sample size calculation formula.

2-2. Intervention

The eligible neonates were randomly assigned (using a computerized random number table generator) into two intervention and control groups. Before the intervention, the purpose and method of the study were described to the parents of the infants and written consent was obtained from them. The intervention group received prophylactic treatment with 2 Gtt/kg (10 mg/kg) acetaminophen drop every 6 hours for 5 days and the controlled group did not receive any intervention.

2-3. Measuring tools

After 10 days, both groups were assessed by echocardiography regarding the PDA condition. Serum levels of ALT and AST enzymes were measured at the beginning of the study and the end of the fifth day of drug use. In case of raising liver enzymes, the drug regimen including 10 mg/kg of acetaminophen was discontinued however the studies have been approved the safety of this dose of acetaminophen (2). In addition, if the arterial duct remained open, patients were treated with the usual regimen including ibuprofen and were reassessed by echocardiography.

2-4. Ethical consideration

The study protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (ID-code: IR.SKUMS.REC.1397.091), and registered at Iranian Registry of Clinical Trials (IRCT: 20190305042935N1).

2-5. Inclusion and exclusion criteria

Neonates with congenital heart defects and major congenital or chromosomal abnormalities, neonates whose mother had a history of using NSAIDs during pregnancy, newborns with hydrops fetalis or increased pulmonary hypertension, neonates with fifth minute Apgar more than 5, neonates with symptomatic PDAs requiring treatment with ibuprofen, newborns with vomiting or hematemesis in the first three days of birth, and newborns with high levels of liver enzymes were all excluded.

2-6. Data Analyses

The results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t test or Mann U test. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P-value of <0.05 were considered statistically significant.

3- RESULTS

In this clinical trial, 64 preterm infants with gestational age less than 31 weeks were randomly divided into two groups of 32 intervention and control. The intervention group was treated with prophylactic acetaminophen and the control group received no intervention. The mean gestational age in the intervention and control group was 29.41 ± 1.24 weeks and 29.41 ± 1.24 weeks, respectively, which was not significantly different ($p> 0.05$). There was a significant different in the rate of PDA closure across the two intervention and control groups (84.4% versus 50.0%, $p = 0.007$). After the intervention, open PDA was found in 16 (50%) of neonates in control group and 5 (15.6%) in intervention group that were treated with routine regimen including ibuprofen and echocardiography was performed again after one month. After treatment with ibuprofen, PDA was closed in the remaining 14 patients (87.5%) in the control group and remaining 4 patients (100%) in the intervention group indicating no difference ($p=0.632$).

Comparison of the mean of AST and ALT before and after the intervention (day 5 of treatment) in the studied groups are shown in **Table.1**. Despite no difference was revealed in the serum level of both enzymes preoperatively, the level of enzymes were significantly higher in the intervention group as compared to control group.

Table-1: Comparison of mean AST and ALT levels before and after intervention in the studied groups.

Parameters	Control group	Intervention group,	P- value
Serum AST			
Before	9.87 ± 1.43	10.53 ± 1.79	0.111
After	9.03 ± 1.12	9.90 ± 1.42	0.012
Serum ALT			
Before	14.65 ± 2.81	15.56 ± 2.93	0.176
After	14.03 ± 2.83	15.37 ± 2.85	0.057

AST: Aspartate transaminase; ALT: Alanine aminotransferase.

4- DISCUSSION

This study was conducted to investigate the impact of acetaminophen prophylaxis on PDA in preterm infants. There was a significant different in the rate of PDA closure across the two intervention and control groups. After the intervention, open PDA was found in 50% of neonates in control group and 15.6% in intervention group. PDA was closed in 87.5% of the control group and all infants in the intervention. The changes in liver enzymes slightly changed after intervention. Based on the scientific sources, PDA remains open in 30-60% of infants with very low weight (7). In this study, 50% of infants in the control group had open arterial duct, while in the intervention group, it was 15.6%, which was significantly lower than the control group, suggesting high effectiveness of the appropriate preventive treatment with acetaminophen. In this study, the infants who had their arterial duct still open after 10 days (16 in the control and 4 in the intervention group) were treated with routine medication (ibuprofen) underwent echocardiography one month later indicating this fact that acetaminophen prophylaxis not only has efficacy in the closure of the arterial duct but also improves the routine treatment efficiency by ibuprofen. Concomitantly with our study, in a study by Akbari Asbagh et al. in 2015, the preventive use of acetaminophen with the dose of 15 mg/kg at 6-hour intervals for 48 hours resulted in arterial duct closure in 75% of premature infants, while only in 50% of control group indicating no statistical difference between the two group probably due to small sample size as well as shorter period of prophylaxis (2). In Bagheri et al.' study, 180 neonates with gestational age less than 34 weeks were divided into intervention and control groups. Acetaminophen prophylaxis was started at an initial dose of 20 mg/kg and maintained at a dose of 7.5 mg/kg at 6-hour intervals for three days. After intervention, PDA remained observable 15% in the intervention group and 71.25% in control group. The prevalence of PDA in the intervention group was significantly lower than the control group. There was also no significant difference in the need for mechanical ventilation or short term mortality in both groups (13). In a systematic review and meta-analysis study by Ohlsson et al. in 2018, the studies were conducted on the administration of acetaminophen prophylaxis, which included a total of 80 premature infants.

Based on the results, the rate of PDA closure after 4 to 5 days was more in placebo group as compared to using acetaminophen, yet with high heterogeneity requiring further studies on premature infants (5). The efficacy of acetaminophen in the treatment of premature neonates with PDA confirmed by echocardiography has been observed in a large number of studies in recent years. In a study by Bardanzellu et al. in 2013, 10 preterm infants with a gestational age of less than 32 weeks with PDA treated with acetaminophen at a concentration of 15 mg at 18-hour intervals for 72 hours. Finally, it was observed that open arterial duct was closed in all patients (20).

In a study by Sinha et al. in 2013, 10 preterm infants suffering PDA with a gestational age of 27 to 33 weeks were treated with acetaminophen at a dose of 15 mg at 8-hour intervals for 48 hours. The results indicate that the arterial duct closes after 72 hours in all infants. In addition, no adverse effects were observed in neonates (9). In a study by Dang et al. in 2013, 80 neonates with gestational age less than 34 weeks and PDA-approved by echocardiography were treated with acetaminophen (15 mg/kg at intervals of 6 hours for 3 days) and based on the results in 81.2% arterial duct closed (14).

In 2014, Oncel et al. treated 45 neonates with gestational age of less than 30 weeks and weighing less than 1200 grams with acetaminophen (15 mg/kg every 6 hours for 3 days) that closure of arterial duct occurred in 72.5% of preterm infants. After retreatment by ibuprofen, PDA remained close in two patients requiring surgery (7). Treatment with a dose of 60 mg/kg/day of acetaminophen in the study by Yurttutan et al. in 2013 caused PDA closure in 5 of 6 premature infants aged 26-33 weeks (11). In a study by Ozdemir et al. in 2013 in 5 of 7 premature infants aged 23-32 (8), in Jasani et al. study in 2013, 6 out of 6 preterm infants aged 28-31 weeks (15), and in a study by Kessel et al. in 2014, 7 out of 7 premature infants (24-28 weeks) (16) benefited from acetaminophen. Acetaminophen is an analgesic and anti-inflammatory drug with poor anti-inflammatory properties, commonly used for analgesic effects in all age groups (2). The safety of low doses of this drug has been shown in preterm infants and it has been reported that in some cases it can reduce hyperbilirubinemia (12, 17). The mechanism of action of acetaminophen in the closure of the arterial duct is still not well defined. Researchers have reported that acetaminophen is effective in inhibiting prostaglandin synthase (18). Prostaglandin synthase has two different catalytic activity including cyclooxygenase and peroxidase activity. The cyclooxygenase activity catalyzes the conversion of arachidonic acid to PGG2 and peroxidation activity of arachidonic acid to PGH2. Cyclooxygenase inhibitors such as indomethacin and ibuprofen with arachidonic acid are competing for cyclooxygenase (19).

Closure of PDA in term neonates is associated with increased blood oxygen and decreased activity of vasodilators, including prostaglandin E2 and I2. Therefore, the treatment of premature infants by the use of cyclooxygenase inhibitors such as indomethacin and ibuprofen, by reducing prostaglandins, accelerates the closure of the arterial duct (14). Therefore, with regard to the activity of inhibition of prostaglandin synthase by acetaminophen, it seems that the efficacy of this drug is also related to inhibition of prostaglandins (16). Before intervention, the mean level of AST and ALT was not significantly different in the intervention and control groups. But after intervention, there was a significant difference between the two groups. Although this difference seems to be significant because the initial values of AST and ALT enzymes in the

control group were slightly higher than the intervention group. It is therefore advisable to consider changes in enzymes in each group. However, these differences are not significant and they are not clinically important because no enzyme increase was seen in any of the groups. In 2017, Bardanzellu et al. concluded that the results of various studies generally indicated the effectiveness of acetaminophen in the treatment of PDA in preterm infants. However, the use of acetaminophen in a number of studies has been associated with an increase in transient liver enzymes as a side effect (20). Ohlsson et al. stated that in a number of studies, serum levels of creatinine and bilirubin were lower in neonates receiving acetaminophen than in infants receiving ibuprofen. Additionally, platelet count and daily urine output were higher in the acetaminophen group than in the ibuprofen group. The researchers also reported that the risk of gastrointestinal bleeding in infants receiving ibuprofen is higher (5). However, it is imperative that long-term safety of the drug confirmed by the follow-up of newborns before acetaminophen is introduced as a safe drug for the treatment or prophylactic treatment of the arterial duct.

4-1. Limitations of the study

The study was conducted only in a local hospital and the results should be generalized with caution.

5- CONCLUSION

The results of this study showed that preventive treatment with 10 mg acetaminophen at 6-hour intervals for 5 days caused PDA closure in 84.4% of immature infants which was significantly higher than control group (50%). Neonates with open PDA (16 in the control and 4 in the intervention group) were retreated with ibuprofen leading PDA closure in 14 patients in the control group and 4 in the intervention group.

6- ACKNOWLEDGEMENTS

The study was financially supported by Shahrekord University of Medical Sciences (grant number: 2733).

7- CONFLICT OF INTEREST: None.

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