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Injectable Acetaminophen Effectiveness in Closing Patent Ductus Arteriosus in Term Infants Hospitalized in the Neonatal Intensive Care Unit

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Abstract

Background: Patent ductus arteriosus is a short path of fetal blood circulation through the lungs that is necessary to maintain life inside the womb. Although this duct should be closed right after birth, in some cases, it remains open and may cause life threatening complications. The present study was conducted with the aim of investigating the effectiveness of injectable acetaminophen in closing patent ductus arteriosus in term infants.

Methods: This study was conducted as a randomized, blinded clinical trial on 80 infants diagnosed with patent ductus arteriosus in the neonatal intensive care unit in Afzalipur Hospital, Kerman. The infants were randomly divided into control and intervention groups. The intervention group received injectable acetaminophen at a dose of 20 mg based on weight in the first hour and 10 mg based on weight every six hours for three days after receiving the initial dose. And the placebo group received 10% dextrose serum equal to acetaminophen amount with the same treatment intervals. Echocardiography was performed again in both groups after three days and the state of PDA closure was evaluated.

Results: Gestational age averages in the intervention and control groups were 37.88 ± 0.13 weeks and 37.95 ± 0.15 weeks, respectively (P=0.738); and the birth weight averages were 2996 ± 83.41 grams and 64.09 ± 2982 grams, respectively (P=0.899). The male gender in the intervention group (57.5%) was higher than that in the control group (40%) (P=0.158). The most common cause of hospitalization of newborns in the intervention and control groups was TTN (Transient Tachypnea of the newborn) (75.0% and 67.5%, respectively) and NAS (Neonatal Abstinence Syndrome) (15.0% and 20.0%, respectively) (P=0.985). In the intervention group with injectable acetaminophen, 85.5% of infants had their PDA closed after receiving the first course of acetaminophen, while this rate was 0.65% in the control group (P=0.016).

Conclusion: Based on the results of this study, injectable acetaminophen can effectively improve PDA disorder of term babies. While the effectiveness of routine drugs used in the treatment of this disorder decreases with increasing infants' age, injectable acetaminophen showed its beneficial effects significantly.

Key Words: Injectable Acetaminophen, Patent Ductus Arteriosus, Premature Baby, Term Baby.

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1- INTRODUCTION

Ductus Arteriosus (DA) is the connection between the pulmonary artery and the descending aorta during the fetal period, through which the deoxygenated blood is directed and enters to the right atrium of the heart for reoxygenation to the placenta. Although the existence of the arterial duct is very necessary for the fetus, this duct undergoes contraction after birth and usually within 72 hours will be physiologically closed and fibrosed; if this active contraction does not occur after birth, the ductus arteriosus will remain open (1). Patent Ductus Arteriosus (PDA) is one of the cardiac disorders that can cause adverse complications such as intracerebral hemorrhage, necrotizing enterocolitis and pulmonary dysplasia in infants. Recently, due to the elevation of the survival rate of premature infants, its incidence rate has increased and it is known as a common complication in 55% of low birth weight and premature babies (2). It's abnormal if the duct remains open in the first weeks after birth. The physiological effect and clinical importance of PDA depend on its size and the cardiovascular status of the patient. PDA may not show any clinical symptoms; however, it can be incidentally detected by echocardiography for various reasons. Regardless of the duct size, complications can occur; and it is important for cardiologists to have the knowledge about the pathophysiology, clinical implications, and management of PDA (3).

PDA with the mechanism of creating a left-to-right shunt and increasing pulmonary artery blood flow causes congestion and pulmonary edema; therefore, disrupts oxygen exchange in a way that the baby may need to be supported by a ventilator. Long-term mechanical ventilation is associated with increased risks of bronchopulmonary dysplasia (2, 4). On the other hand, the continuation of PDA increases the incidence of intraventricular bleeding, hypoperfusion of the splanchnic network, and increases the risk of necrotizing enterocolitis (4, 5). Other symptoms include excessive shunt from arterial to pulmonary circulation, Systolic or continuous murmur, low diastolic pressure, wide pulse pressure, low blood pressure, narrow pulse, high serum creatinine concentration or oliguria, hepatomegaly and signs of pulmonary edema. Also, tachypnea decrease in oxygen saturation and the increase in respiratory support are considered (6). Despite the various randomized and controlled descriptive and charismatic studies that are conducted in the field of PDA diagnosis and management, there is still no general consensus in this field, due to the risks of these methods that should also be considered along with their benefits (7). PDA can cause heart failure or endocarditis; therefore, it is necessary to close it by surgical and non-surgical methods such as hemoglobin correction, fluid and sodium restriction, using Amplatzer or coil during angiography, indomethacin, nitric oxide synthesis inhibitors, and ibuprofen (8-10).

Cyclooxygenase (COX) inhibitors, such as indomethacin and ibuprofen are among the drugs that are used in PDA treatment (7, 11), which may carry the risk of severe side effects, such as visceral vasoconstriction, gastrointestinal bleeding, inhibition of platelet aggregation, and kidney failure (12).

Recently, studies conducted in the field of using oral acetaminophen (paracetamol) instead of ibuprofen to close PDA have increased (13, 14). Acetaminophen inhibits prostaglandin synthesis by affecting the peroxidase part of the enzyme. Peroxidase is activated with peroxide concentration 10 times lower than cyclooxygenase, and with this premise, acetaminophen can be a more effective drug in the treatment of PDA (15,

16), so that more than 25% of very premature infants with PDA are treated with acetaminophen (17).

Oral acetaminophen has advantages such as being cheaper in terms of intravenous preparation (18). On the other hand, it can reduce the need for surgical methods and catheterization and their complications. Therefore, the present study was conducted with the aim of investigating the effectiveness of injectable acetaminophen in closing patent ductus arteriosus in term infants.

2- MATERIALS AND METHODS

2-1. Design and sampling

This study was conducted as a randomized, blinded charismatic clinical trial on term infants in the neonatal intensive care unit of Afzalipur Hospital, Kerman from 2020 to 2021.

2-1.1. Inclusion and exclusion criteria

Inclusion criteria included gestational ages equal or greater than 37 weeks; and postpartum ages of 3 to 28 days, diagnosed with PDA. In order to confirm the diagnosis of PDA in infants who had clinical signs of open ductus arteriosus such as wide pulse pressure, tachypnea, and oxygen dependence during their first visit (6), echocardiography was performed on the third day after birth by a cardiologist. Exclusion criteria included parents not willing for their baby to participate in the study, infants with other congenital heart diseases, multiple anomalies, life threatening diseases and asphyxia.

2-1.2. Sample size

In this regard, the estimated frequency of PDA closure in the intervention group (α=0.05, β=0.2) is 80% (p1=0.8) and in the placebo group 50% (p2=0.5); the minimum clinically significant difference in pain intensity in the two groups 30% (Δ=0.3) and the sample size in the groups was considered equal to 40.

$$n_1 = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times (p_1^2 + \frac{p_2^2}{k})}{\Delta^2}, n_2 = k \times n_1$$

2-2. Procedure

Infants were selected by available sampling method including the infants eligible for the study who were diagnosed with PDA and admitted to the Neonatal Intensive Care Unit in Afzalipur Hospital in Kerman from 2020 to 2021. After taking informed consent from the parents, the infants were divided into intervention and control groups. For this purpose, two codes- 1 and 2- were placed in separate envelopes, and these envelopes were placed in a box. After that, a code was randomly chosen for each baby, and the baby was placed in the group related to the code (code 1 of the acetaminophen intervention group and code 2 of the control group). The intervention group received injectable acetaminophen at a dose of 20 mg based on weight in the first hour and 10 mg based on weight every six hours for three days after receiving the initial dose. On the other hand, the placebo group received 10% dextrose serum equal to acetaminophen amount with the same treatment intervals. After 3 days from the beginning of the study, echocardiography was performed for both acetaminophen intervention and control groups again and PDA status was also evaluated. Echocardiography was performed by a pediatric cardiologist using a SAMSUNG device. HM70 EVO; Korea. The required date such as gestational age, infant's birth weight, infant's gender, labor method, and the reason for hospitalization were collected using a checklist.

2-3. Data Analysis

The collected data were analyzed after coding by SPSS version 22 statistical software. Frequency, percentage, mean and standard deviation were used to

describe the data. First, the assumption of normality of data frequency distribution was checked by Kolmogorov-Smirnov test and analyzed by chi-square ($\chi 2$) and independent t tests. The significance level was considered less than 0.05.

3- RESULTS

In this study, 80 term infants with PDA who were admitted to the intensive care unit were divided into two groups, intervention group with injectable acetaminophen with a sample size of 40 babies and a control group treated with placebo with a sample size of 40 babies. The average gestational ages in the intervention and control groups were 37.88 ± 0.13 weeks and 37.95 ± 0.15 weeks, respectively (P=0.738). The average birth weight of infants in the intervention group was 2996 ± 83.41 grams and in the control group was 2982 ± 64.09 grams (P=0.899). Although the gender rate in the intervention group (57.5%) was higher than that of the control group (40%), the difference was not statistically significant (P=0.158). In both intervention and control groups, the frequency of cesarean delivery was higher (85.7% and 75%, respectively) (P=0.871). The most common reason of newborns' admission in the intervention group with injectable acetaminophen and the control group was TTN (Transient Tachypnea of the newborn) (75.0% and 67.5% respectively) then NAS (Neonatal Abstinence Syndrome) (15.0% and 67.5% respectively) 0.20 percent (P=0.985).

The results of injectable acetaminophen effectiveness in closing patent ductus arteriosus in term infants are shown in Table 1 and 2.

The results of echocardiography, three days after the study, showed that in the intervention group with injectable acetaminophen, 85.5% of infants had closed PDA after receiving the first course of acetaminophen, while this rate was 0.65% in the control group. Also, 19.5% of infants in the intervention group had their PDA closed after receiving the second course of injectable acetaminophen (P=0.016).

Table-1: Frequency distribution of demographic and background variables in term infants in Afzalipur Medical Education Center, Kerman

Variables	Integral group (n=40)	Control group (n=40)	P-value
Gestational age (weeks)*	13.0+88.37	15.0+95.37	0.738
Newborn's weight (grams)*	42.83+2996	09.64+2982	0.899
**Gender Male	(5.57 %) 35	(40 %) 16	0.158
female	(5.42 %) 17	(60 %) 24	-
**Delivery method cesarean	(7.85 %) 35	(75 %) 30	0.871
Vaginal delivery	(5.14 %) 5	(25 %) 10	-
**Admission reason TTN¥	(75 %) 30	(5/67 %) 27	0.985
Pneumonia	(10 %) 4	(5/12 %) 5	-
NAS£	(15 %) 6	(20 %) 8	-

* The values are in the form of standard deviation of the mean, independent t-test and significance level of 0.05.

** Values are in the form of number (percentage), chi-square test and significance level 0.05.

¥ Transient Tachypnea of the newborn

£ Neonatal Abstinence Syndrome

Table-2: investigating the effectiveness of injectable acetaminophen in closing PDA in term newborns

Variables	Integral Group (40 people) frequency (percent)	Control Group (40 people) frequency (percent)	P-value
PDA closure after the first course	(5.80 %) 33	(65 %) 23	0.016
PDA closure after the second course	(5.19 %) 7	(35 %) 17	-

* Values are in the form of number (percentage), chi-square test and significance level 0.05.

4- DISCUSSION

PDA is the failure to close the ductus arteriosus, which disturbs venous blood circulation, for which different treatment methods have been mentioned over the past years (19). Before using corticosteroids during pregnancy, PDA was frequently found in preterm infants of all gestational ages and was associated with respiratory distress syndrome. The standard treatment was with indomethacin and several studies suggested the benefits of early PDA closure (20). With the improvement in ventilation strategies, using prenatal corticosteroids, exogenous surfactant and waiting for the spontaneous closure of the ductus arteriosus and other treatment methods were suggested (21). Intravenous acetaminophen prescription as traditional Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in PDA closure with less toxicity has attracted the attention; also, being along with unstable and transient elevation of liver enzymes, it has been reported as a side effect.

The results of this study showed that injectable acetaminophen is effective in closing PDA in term infants. Echocardiography examination of infants three days after receiving the first course of injectable acetaminophen showed that PDA was closed in 85.5% of infants. In newborns who suffer from hypoxia and acidosis, the ductus arteriosus can be closed with a delay; however, if this process continues for a long time, it can lead to heart failure. Therefore, it is necessary to perform therapeutic interventions in this field. Preterm newborns with PDA are treated with various drugs such as indomethacin, ibuprofen, and acetaminophen (16, 22-24). The results of Bagheri et al.'s (18) study showed that in preterm newborns injectable paracetamol can be a suitable alternative for medicines such as ibuprofen and indomethacin for PDA closure. In a systematic review and network meta-analysis of 64 clinical and observational charisma studies on 14,568 term and preterm infants with PDA using indomethacin, ibuprofen, acetaminophen, placebo or no specific intervention, the results showed that treatment with Indomethacin, ibuprofen, or acetaminophen (with moderate, high, and low quality evidence, respectively) is effective in closing PDA and limiting the use of surgery to close PDA. Ibuprofen reduced the risk of intraventricular hemorrhage and oliguria compared to indomethacin. Administration of acetaminophen also had a lower risk of oliguria compared to indomethacin (11). In another meta-analysis in 2022, the efficacy and safety of oral acetaminophen for premature infants with PDA were investigated in 16 clinical charisma studies, and the results showed that there is no significant difference in the effectiveness of oral acetaminophen and ibuprofen or indomethacin in premature infants with PDA. However, compared to ibuprofen, oral acetaminophen may reduce

the incidence of oliguria and gastrointestinal bleeding (25). Therefore, injectable acetaminophen (paracetamol) can be an effective alternative to indomethacin or ibuprofen with less side effects to induce PDA closure (26). In McPherson et al.'s study, the results indicated the beneficial effect of using acetaminophen in preterm infants on PDA closure, and no correlation was observed between the serum concentration of acetaminophen following intravenous treatment and ductal response or hepatotoxicity (27). There are multiple reasons for PDA closure after birth and it has been shown that the elevation of arterial blood oxygen pressure that occurs along with lungs ventilation after birth leads to the closure of this duct. Meanwhile, the role of some prostaglandins is also approved, in fact, the balance between the oxygen-constricting and prostaglandin-expanding effects on arterial relaxation plays a fundamental role (28). Two types of cyclooxygenase inhibitors that are commonly used in most of the countries to close the patent ductus arteriosus are indomethacin and ibuprofen, in which each of them has its advantages and disadvantages. Moreover, due to the high costs of these drugs, most of the medical centers prefer to include only one of these two drugs in their treatment plan. However, both drugs' success rate is close to each other when their standard dose is used (9, 29, 30). Injectable acetaminophen (paracetamol), which is a prostaglandin synthesis inhibitor, has been effectively used in the treatment of patent ductus arteriosus in premature infants, and few side effects have been reported (31). On the other hand, the effects of drugs used for PDA treatment depend on the intrauterine age of the baby; the duct's sensitivity toward the effects of prostaglandins is greater in preterm infants and it decreases with age (32). Therefore, despite the negative effects of increasing the age of the baby in reducing the effectiveness of drugs on PDA, it seems that injectable acetaminophen has been able to effectively improve this disorder.

4-1. Limitations of the study

The main limitation of the current study is the lack of data collection on the side effects of injectable acetaminophen, which can be considered in future studies.

5- CONCLUSION

According to our results, injectable acetaminophen could effectively improve PDA disorder in term infants. Although the effectiveness of routine drugs used in the treatment of this disorder, such as indomethacin and ibuprofen, decreases with age, injectable acetaminophen significantly exerted its beneficial effects and was effective in a high percentage of babies.

6- ETHICAL CONSIDERATIONS

This clinical trial was approved by the Ethics Committee of Kerman University of Medical Sciences with the code IR.KMU.AH.REC.1400.243 and registered in the Iranian Clinical Trials Registration Center with the code IRCT20230219057459N1.

7- REFERENCES

1. Fanaroff AA, Martin RJ. Neonatal-perinatal medicine: diseases of the fetus and infant. Elsevier; 2020.

2. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics. 2006 Apr 1;117(4):1113-21.

3. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation. 2006 Oct 24;114(17):1873-82.

4. Jaleel MA, Rosenfeld CR. Patent ductus arteriosus and intraventricular hemorrhage: a complex association. The Journal of pediatrics. 2013 Jul 1;163(1):8-10.

5. Patel BK, Shah JS. Necrotizing enterocolitis in very low birth weight infants: a systemic review. International Scholarly Research Notices. 2012;2012(1):562594.

6. Gillam-Krakauer M, Reese J. Diagnosis and management of patent ductus arteriosus. Neoreviews. 2018 Jul 1;19(7):e394-402.

7. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. Jama. 2018 Mar 27;319(12):1221-38.

8. Keller RL, Tacy TA, Fields S, Ofenstein JP, Aranda JV, Clyman RI. Combined treatment with a nonselective nitric oxide synthase inhibitor (l-NMMA) and indomethacin increases ductus constriction in extremely premature newborns. Pediatric research. 2005 Dec;58(6):1216-21.

9. Thomas RL, Parker GC, Van Overmeire B, Aranda JV. A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. European journal of pediatrics. 2005 Mar;164:135-40.

10. Meraji M, Nouri NM, MEHR ALIZADEH S, Aarabi Moghadam MY. Transcatheter occlusion of pda by detachable coil occluder and amplatzer device. Iranian Heart Journal. 2005 Mar 1;6(1.2):43-7.

11. Marconi E, Bettiol A, Ambrosio G, Perduca V, Vannacci A, Troiani S, et al. Efficacy and safety of pharmacological treatments for patent ductus arteriosus closure: a systematic review and network meta-analysis of clinical trials and observational studies. Pharmacological research. 2019 Oct 1;148:104418.

12. Yekta Oncel M, Erdeve O. Safety of therapeutics used in management of patent ductus arteriosus in preterm infants. Current drug safety. 2015 Jul 1;10(2):106-12.

13. Nadir E, Kassem E, Foldi S, Hochberg A, Feldman M. Paracetamol treatment of patent ductus arteriosus in preterm infants. Journal of Perinatology. 2014 Oct;34(10):748-9.

14. Terrin G, Conte F, Oncel MY, Scipione A, McNamara PJ, Simons S, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2016 Mar 1;101(2):F127-36.

15. Al-Lawama M, Alammori I, Abdelghani T, Badran E. Oral paracetamol versus oral ibuprofen for treatment of patent ductus arteriosus. Journal of International Medical Research. 2018 Feb;46(2):811-8.

16. Oncel MY, Yurttutan S, Uras N, Altug N, Ozdemir R, Ekmen S, et al. An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2013 Jan 1;98(1):F94-.

17. Esmaili H, Bahreynian M, Qorbani M, Motlagh ME, Ardalan G, Heshmat R, et al. Prevalence of general and abdominal obesity in a nationally representative sample of Iranian children and adolescents: the CASPIAN-IV study. Iranian journal of pediatrics. 2015 Jun;25(3).

18. Bagheri MM, Niknafs P, Sabsevari F, Torabi MH, Bijari BB, Noroozi E, et al. Comparison of oral acetaminophen versus ibuprofen in premature infants with patent ductus arteriosus. Iranian journal of pediatrics. 2016 Aug;26(4).

19. Dang D, Wang D, Zhang C, Zhou W, Zhou Q, Wu H. Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial. PloS one. 2013 Nov 4;8(11):e77888.

20. Mosalli R, AlFaleh K. Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants. Cochrane Database of Systematic Reviews. 2008(1).

21. Nemerofsky SL, Parravicini E, Bateman D, Kleinman C, Polin RA, Lorenz JM. The ductus arteriosus rarely requires treatment in infants> 1000 grams. American journal of perinatology. 2008 Nov;25(10):661-6.

22. Oncel MY, Yurttutan S, Degirmencioglu H, Uras N, Altug N, Erdeve O, et al. Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. Neonatology. 2013 Mar 1;103(3):166-9.

23. Oncel MY, Yurttutan S, Erdeve O, Uras N, Altug N, Oguz SS, et al. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. The Journal of pediatrics. 2014 Mar 1;164(3):510-4.

24. Yurttutan S, Oncel MY, Arayıcı S, Uras N, Altug N, Erdeve O, et al. A different first-choice drug in the medical management of patent ductus arteriosus: oral paracetamol. The Journal of Maternal-Fetal & Neonatal Medicine. 2013 May 1;26(8):825-7.

25. Zi-Yun X, Ruo-Lin Z, Yue-Wei X, Tao B. Efficacy and safety of oral acetaminophen for premature infants with patent ductus arteriosus: a meta-analysis. Frontiers in Pharmacology. 2022 Jan 18;12:696417.

26. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database of Systematic Reviews. 2018(4).

27. McPherson C, Luecke CM, Liviskie CJ, Zeller BN, Vesoulis ZA. Acetaminophen serum concentrations in infants treated intravenously for patent ductus arteriosus. The Journal of Pediatric Pharmacology and Therapeutics. 2019 Mar 1;24(2):134-7.

28. Conrad C, Newberry D. Understanding the pathophysiology, implications, and treatment options of patent ductus arteriosus in the neonatal population. Advances in Neonatal Care. 2019 Jun 1;19(3):179-87.

29. Lago P, Bettiol T, Salvadori S, Pitassi I, Vianello A, Chiandetti L, et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. European journal of pediatrics. 2002 Apr;161:202-7.

30. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, De Groote K, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. New England Journal of Medicine. 2000 Sep 7;343(10):674-81.

31. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. Pediatrics. 2011 Dec 1;128(6):e1618-21.

32. Supapannachart S, Limrungsikul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi Hospital. Journal of the Medical Association of Thailand= Chotmaihet thangphaet. 2002 Nov 1;85:S1252-8.