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The Effect of Rectal Acetaminophen on the Closure of Ductus Arteriosus in Premature Neonates: A Case Series Study

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ABSTRACT

Background: Patent Ductus Arteriosus (PDA) with 30% prevalence is regarded as a common and threatening condition in premature neonates.
Objectives: The present study aimed to assess the effect of rectal acetaminophen on PDA treatment in premature neonates.
Methods: This case series study was conducted on all premature neonates with PDA admitted in Neonatal Intensive Care Unit (NICU) in Dr. Mohammad Kermanshahi Hospital affiliated to Kermanshah University of Medical Sciences (KUMS) during one year (2017). The subjects had contraindications for simultaneous administration of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and oral medications. Finally, 18 neonates (nine males and nine females) were studied. The patients were treated with 25 mg/kg rectal acetaminophen as the loading dose followed by 15 mg/kg/8 h for three days. Diagnosis and correction of PDA before and after the treatment were justified by echocardiography. Finally, statistical analyses were performed using chi-square and Mann-Whitney tests.
Results: About 95% of the neonates responded to the treatment, while the response rate for oral ibuprofen and oral acetaminophen was 70 - 75% based on the results of the previous studies. The results indicated no statistically significant relationships among gestational age, birth weight, and the time of using rectal acetaminophen in two treatment steps of the study (P values = 0.898, 0.281, and 0.219, respectively).
Conclusion: Rectal acetaminophen is suggested as an influential, safe, and cost-effective therapeutic option for PDA closure in preterm neonates with gestational age < 35 weeks.

1. Background

Patent Ductus Arteriosus (PDA) is considered to be a common and life-threatening condition, which is prevalent in more than 30% of neonates with birth weight < 1500 g (1). PDA can also occur in up to 60 - 80% of premature neonates with gestational age less than 28 weeks (2). It results in some significant changes in blood supply of the brain, kidneys, intestine, and lungs, and exacerbates conditions, such as Respiratory Distress Syndrome (RDS), Broncho Pulmonary Dysplasia (BPD), Necrotizing Enterocolitis (NEC), Intraventricular Hemorrhage (IVH), Retinopathy of Prematurity (ROP), and pulmonary hemorrhage, due to continuous left to right shunt through hemodynamic disturbances. Finally, it increases morbidities, mortalities, and need for ventilation (3, 4). Burnard realized the relation between heart murmur of PDA and the intensity of its complications about fifty years ago. Jegier invented the surgical closure of PDA and Friedman suggested the pharmacological treatment of PDA by Cyclooxygenase Inhibitors (COIs) like indomethacin and ibuprofen, which have been used around the world (4). These drugs act through inactivating the cyclooxygenase-dependent part of prostaglandin synthesize H2 complex, which prevents arachidonic acid conversion to prostaglandin G2. In this way, prostaglandin G2 is not converted to prostaglandin

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H2, leading to the impediment of prostaglandin F2α, E2, I2, and thromboxane A2 synthesis. This process results in contraction of vascular smooth muscles and reduction of oxygen in supplying vessels and angiogenesis. These, in turn, lead to regeneration of ductus arteriosus intima and apoptosis and aggregation of platelets that causes obstruction, fibrosis, and anatomical closure of ductus arteriosus (5). Intravenous or oral ibuprofen and indomethacin (NSAIDs) in specific doses are routinely used to heal PDA (6). Thus, due to different limitations in using COIs, diverse complications, and high price of intravenous forms, it is rational to find safer and more applicable substitutes with lower complications. The contraindications of COIs include oliguria, IVH, NEC, thrombocytopenia (less than 60000) with active bleeding, hyperbilirubinemia with intensive phototherapy, and the symptoms of oral or gastrointestinal use intolerance. In addition, the complications related to using COIs include peripheral vascular contraction, increase in the possibility of NEC, IVH, renal failure, hyperbilirubinemia with blood change, Chronic Lung Disease (CLD), and active gastrointestinal and systemic hemorrhage due to platelet dysfunction (1, 3-8). The success rate of PDA treatment by COIs was reported to be 70 - 85% (1, 2, 5, 7). Hammerman et al. reported the PDA closure after using oral acetaminophen as a casual finding leading to the use of this drug (7), because acetaminophen has been used as an anti-inflammatory and analgesic treatment in neonates for years due to such features as safety, low price, accessibility, and lack of limitations and complications related to NSAIDs. However, the safe and effective dose of acetaminophen in premature neonates is unclear and the mechanism of its effect on PDA closure remains a hypothesis. In the latest textbooks of neonatology, the effective and safe application of acetaminophen on PDA closure has been highlighted although more studies should be conducted to achieve complete and reliable results (4, 6, 8). A large body of studies has been done by using oral acetaminophen, while rectal ibuprofen was only utilized in one trial to determine its efficacy in PDA closure compared to indomethacin (9). To the best of our knowledge, no study has focused on the role of rectal acetaminophen in PDA closure in preterm neonates. As NSAIDs or oral therapy is contraindicated in neonates with PDA, the only lifesaving intervention can be related to rectal acetaminophen in a safe, easily accessible, and low price form.

2. Objectives

The present study aims to evaluate the efficacy of rectal acetaminophen in PDA closure in premature neonates with gestational age < 35 weeks.

3. Patients and Methods

The present case series was conducted at Dr. Mohammad Kermanshahi Hospital as the only specialized pediatric hospital in Kermanshah province during one year (2017). During this one year, 68 newborns were admitted with PDA confirmed by echocardiography. According to Table 1, only 18 neonates met the inclusion criteria of the study (PDA with internal diameter over 1.5 mm and AO/LA over 1.6, significant hemodynamic instability, and contraindications for NSAIDs and oral administration of drugs). The patients were treated with 25 mg/kg rectal acetaminophen as the loading dose followed by 15 mg/kg/8 h for three days (1 loading dose + 9 maintenance doses = 10 doses). In case of incomplete relief of PDA, the second course of treatment was applied similar to the first course, except for the loading dose (25 mg/kg). If the ductus remained open after the second course of treatment, the intervention would be considered as failed. Diagnosis and correction of PDA before and after the treatment were justified via echocardiography. In addition, the possibility of complications or contraindications of acetaminophen administration before and after the treatment was evaluated by proper para clinical measurements (Complete Blood Count (CBC-diff), Aspartate Transaminase (AST), Alanine Transaminase (ALT), Bilirubin (Bili), Na, K, and serum

Table 1. The Inclusion and Exclusion Criteria for Rectal Acetaminophen Treatment in Neonates with PDA

Inclusion Criteria
1. GA < 35 weeks with significant PDA (intra ductal diameter ≥ 1.5 mm and left atrium/aortic root diameter > 1.6 mm)
2. Contraindications for NSAIDs use (platelets < 60000/mm ^{3}, active bleeding, GI bleeding, serum creatinine > 1.5 mg/dL, oliguria, and suspected NEC)
3. Contraindications for oral therapy (NEC, orofacial anomalies, upper respiratory or GI anomalies, intolerance of oral therapy due to nausea and abdominal distention, post CPR or surgery, hypoxia and encephalopathy, severe respiratory distress and respiratory rate > 80/minutes, postictal phase, hemodynamic instability, and shock)
Exclusion criteria
1. Rectosigmoid anomalies
2. Neutropenia < 1500 mm ^{3}
3. Platelets < 20000 mm ^{3}
4. NEC
5. IVH (grades 3 and 4)
6. Hepatic failure or increase in liver enzymes
7. Hemodynamic instability and shock
8. Severe sepsis
9. GI perforation or bleeding
10. Hyperbilirubinemia requiring blood exchange
11. Renal failure or oliguria with creatinine clearance <10%

Abbreviations: GA, gestational age; PDA, patent ductus arteriosus; GI, gastrointestinal; NEC, necrotizing enterocolitis; CPR, cardiopulmonary resuscitation; IVH, intraventricular hemorrhage

Creatinine (Cr) concentration).

Because up to the time of this study, premature children with PDA had contraindications for NSAIDs or oral therapy, it was morally impossible to have a comparator group with alternative or placebo treatment. Therefore, this study was performed as a case series and the results were compared to those of the previous studies. The results were also compared in subgroups using chi-square and Mann-Whitney tests.

This study was registered in the Iranian Registry of Clinical Trials (IRCT registration code: IRCT2017020732449N1). Moreover, written informed consent forms were obtained from the neonates' parents.

4. Results

In the present study, 18 premature neonates (nine males and nine females) with PDA received rectal acetaminophen. The mean gestational age, birth weight, and age when receiving rectal acetaminophen (Figure 1) were 32 ± 1.9 weeks, 1730 ± 477 g, and 3.83 ± 2.22 days, respectively. No complications occurred in any of the cases. Only one male neonate with gestational age of 33 weeks and birth weight of 1650 g who had received the first dose of rectal acetaminophen on the second day of birth was expired.

Based on Table 2, no statistically significant relationship was observed among gestational age (P = 0.953), birth weight (P = 0.300), and the time of using rectal acetaminophen (P = 0.244) in first and second treatment steps of the study. As illustrated in Figure 2, 95% of the patients responded to the treatment, while the response rate for oral ibuprofen and oral acetaminophen was 70-75% based on the results of the previous studies (10).

5. Discussion

Symptomatic PDA is considered to be a challenging problem in extremely premature neonates. COIs (ibuprofen and indomethacin) are the most widely prescribed drugs to resolve this problem, which lead to muscular contraction at the ductus arteriosus followed by closure through inhibiting its prostaglandin synthesis. It is worth noting that using these drugs can have side effects and complications, such as renal function disturbance, intestinal hemorrhage or perforation, and platelet aggregation inhibition (5, 11). Therefore, it is necessary to have an alternative treatment with lower complications. Hammerman et al. reported that acetaminophen could be regarded as an appropriate alternative (7). Accordingly, a large number of researchers compared the effects of acetaminophen and COIs in different trials (8, 12-16). The pharmacokinetic and pharmacodynamics of acetaminophen are available

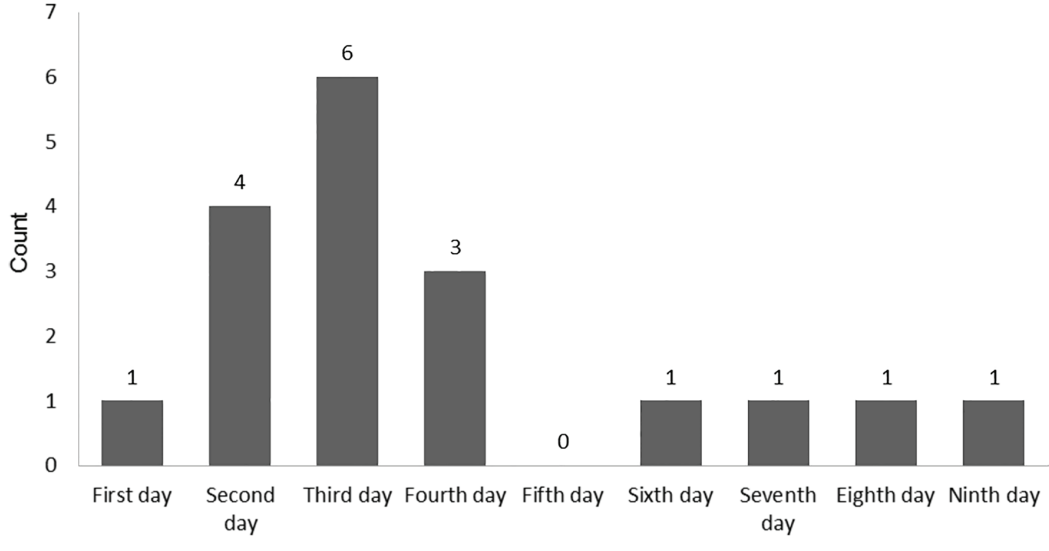

Figure 1. The Frequency of Neonates' Ages at the Time of Rectal Acetaminophen Administration

Table 2. Comparison of the Premature Neonates with PDA based on the Response Stage after Treatment with Rectal Acetaminophen

Subgroups		Response to Treatment (n)	Mean	Standard Deviation	P-value *
Gestational age (weeks)		Response in the first step (14)	32.0	1.8	0.953
Response in the second step (3)			31.7	3.2	
Weight (gram)		Response in the first step (14)	1671.4	457.3	0.300
Response in the second step (3)			2033.3	642.9	
Age at the beginning of treatment (days)		Response in the first step (14)	3.6	2.0	0.244
Response in the second step (3)			5.3	3.2	
			Number	Percent	
Sex	**Male**	Response in the first step	7	87.5	0.547 **
		Response in the second step	1	12.5	
	Female	Response in the first step	7	77.8	
		Response in the second step	2	22.2	

* Based on Mann-Whitney U test. ** Based on Fisher's exact test

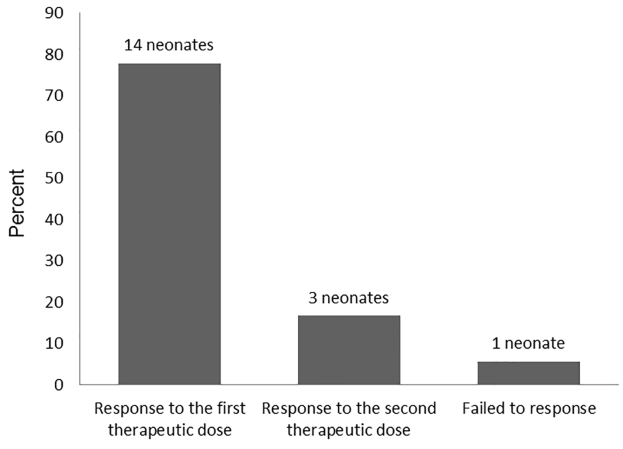

Figure 2. Bar Chart of Response to Rectal Acetaminophen in Premature Neonates with PDA

in neonates and its effective therapeutic dose is 10 mg/L, which is equal to the loading dose of 20 mg/kg Intravenously (IV) or orally and 20 - 40 mg/kg rectally. In addition, the maintenance dose is 10 mg/kg IV or orally and 12 - 18 mg/kg rectally. These doses are applied every six and eight hours in term and preterm neonates, respectively (17-19). This accepted standard was implemented in the present study.

Terrin et al. conducted the first meta-analysis and systematic review on the efficacy of acetaminophen in PDA closure and found that the efficacy of acetaminophen was similar to that of ibuprofen although the results could not be generalized due to some limitations in the neonates population (20). The current study results indicated that rectal acetaminophen was a highly effective therapy without any complications. Nonetheless, the results could not be compared to those of other studies since rectal acetaminophen was used for the first time in this study. Recently, Bardandzellu et al. compared the effects of acetaminophen, NSAIDs, placebo, and no interventions on PDA closure by evaluating all trials performed in 2015 - 2016 (six Randomized Clinical Trials (RCTs) and nine non-controlled trials). They concluded that despite all varieties in the results, acetaminophen was a safe, inexpensive, and highly effective treatment for PDA among neonates (21). The present study focused on all characteristics related to acetaminophen, while Bardandzellu et al. failed to consider rectal acetaminophen in their study.

Roofthooft et al. (22) may be regarded as the only researchers who reported the low efficacy (18%) of acetaminophen in PDA closure in neonates aging more than two weeks. This issue cannot be emphasized in the present study as all neonates were less than 14 days old.

Overall, rectal acetaminophen can be suggested as a new form of therapy due to its easy applicability, safety, and cost-effectiveness as an alternative method for PDA closure by IV or oral acetaminophen explained in different studies (18, 20, 21). Yet, RCTs including larger sample sizes are recommended to be conducted on the issue.

The present work clearly had some limitations. First, the selected patients needed the therapeutic intervention due to hemodynamic instability, including an increase in respiratory distress and cardiac hyper-dynamicity, and an increasing need for cardiac oxygenation. Second, the number of cases decreased due to the patients' contraindication for simultaneous administration of NSAIDs and oral medications. Finally, no control group was considered due to some ethical limitations. However, the sample size was comparable to those of other studies on oral acetaminophen therapy.

5.1. Conclusion

Based on the results, rectal acetaminophen can be suggested as a safe, cost-effective, and influential therapeutic option for PDA closure in preterm neonates with gestational age < 35 weeks.

Ethical issues and conflict of interests.

5.2. Ethics

The present study was approved by the Ethic Committee of Kermanshah University of Medical Sciences (code: 3004175). The authors declare no conflict of interests.

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Authors' Contribution

Study concept and design: MV, HD, AR, and AA. Analysis and interpretation of data: MV, AR, and AA. Echocardiography: HD. Acquisition of data: AR. Drafting of the manuscript: AR. Critical revision of the manuscript for important intellectual content: MV. Statistical analysis: AA. Study supervision: MV.

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