ORIGINAL ARTICLE

Positive tendency toward synchronous use of acetaminophen and ibuprofen in treating patients with patent ductus arteriosus

Patent duktus arteriyozuslu hastaların tedavisinde eş zamanlı asetaminofen ve ibuprofen kullanımına yönelik artmış eğilim

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ABSTRACT

Objective: Spontaneous closure of the ductus arteriosus often fails to occur in premature newborns and this condition can be associated with increased morbidity and mortality. The initial treatment to achieve closure of the opening is pharmacological, and various nonsteroidal anti-inflammatory drugs may be used. The aim of this study was to determine whether combining acetaminophen with ibuprofen is more effective than the individual use of these drugs to treat patent ductus arteriosus (PDA).

Methods: The present randomized, controlled trial study included 154 premature newborns with PDA. The patients were randomized into 3 groups: the acetaminophen group (n=67), ibuprofen group (n=68), and combination drug group (n=19). Echocardiography was performed before initiating the medication and after completing a first and second course of treatment. Blood markers were measured to assess the safety of the 3 types of therapy.

Results: After the first course of treatment, PDA closure was seen in 76.1% of the infants in the acetaminophen group, 76.4% of those in the ibuprofen group, and 78.9% of the combination therapy group (p=0.97). The closure rate after a second course of treatment was 43.7% in the acetaminophen group, 62.5% in the ibuprofen group, and 100% in the combination group. There were no complications attributed to the 3 methods of treatment used.

Conclusion: Concomitant use of acetaminophen and ibuprofen can be an effective option for closure of PDA. Other studies with a larger sample size are recommended in order to confirm these results.

ÖZET

Amaç: Prematüre yenidoğanlarda duktus arteriyozusun kendiliğinden kapanması sıklıkla başarısız olur ve bu durum artmış morbidite ve mortalite ile ilişkilendirilebilir. Açıklığın kapanmasını sağlamak için ilk olarak farmakolojik tedavi uygulanmakta olup çeşitli steroid olmayan anti-enflamatuvar ilaçlar kullanılabilir. Bu çalışmanın amacı, asetaminofeni ibuprofen ile birleştirmenin patent duktus arteriyozus (PDA) tedavisinde bu ilaçların tek tek kullanımından daha etkili olup olmadığını belirlemekti.

Yöntemler: Bu randomize, kontrollü çalışmaya, PDA'lı 154 prematüre yenidoğan alındı. Hastalar 3 gruba randomize edildi: Asetaminofen grubu (n=67), ibuprofen grubu (n=68) ve kombinasyon ilaç grubu (n=19). İlaca başlamadan önce ve birinci ve ikinci tedavi kürünü tamamladıktan sonra ekokardiyografi yapıldı. Üç tedavi yönteminin güvenliğini değerlendirmek için kan belirteçleri ölçüldü.

Bulgular: İlk tedavi küründen sonra asetaminofen grubundaki bebeklerin %76.1'inde, ibuprofen grubundakilerin %76.4'ünde ve kombinasyon tedavi grubunun %78.9'unda PDA'nın kapandığı görüldü (p=0.97). İkinci bir tedavi küründen sonra kapanma oranı asetaminofen grubunda %43.7, ibuprofen grubunda %62.5 ve kombinasyon grubunda %100 idi. Kullanılan üç tedavi yöntemine ilişkin herhangi bir komplikasyon yoktu.

Sonuç: Asetaminofen ve ibuprofenin birlikte kullanımı PDA'nın kapatılmasında etkili bir seçenek olabilir. Bu sonuçları doğrulamak için daha büyük örneklem büyüklüğüne sahip başka çalışmaların yürütülmesi tavsiye edilir.

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Abbreviations:

BPD	*Bronchopulmonary dysplasia*
IVH	*Intraventricular hemorrhage*
NEC	*Necrotizing enterocolitis*
NSAID	*Non-steroidal anti-inflammatory drug*
PDA	*Patent ductus arteriosus*
PG	*Prostaglandin*
PO2	*Partial pressure of oxygen*

The ductus arteriosus is an important vessel in fetal circulation and shunts two-thirds of the cardiac output of the fetus toward the descending aorta. Factors that maintain ductal patency during the fetal period include the low partial pressure of oxygen (PO2), circulating prostaglandins (PG), and local nitric oxide.[1,2]

After birth, an increase in arterial PO2 and a drop in circulating PGE2 are followed by a drop in blood pressure within the lumen of the ductus. This event typically leads to functional closure of the duct within 18 to 24 hours of life and the anatomical closure of the duct over the next few weeks.[2,3] In preterm neonates, the persistence of high levels of circulating PGE2 is a major cause of delayed or nonclosure of the duct. A persistently patent ductus arteriosus (PDA) occurs in 1 of 2000 term births and 8 of 1000 premature births.[1] A left-to-right shunt through ductus arteriosus has been associated with respiratory failure, intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and a decreased survival rate.[3–6]

The first approach to ductus arteriosus closure is pharmacological; however, surgical ligation is performed in patients with drug failure or a drug contraindication.[7] The standard line of medical therapy is non-steroidal anti-inflammatory drugs (NSAIDs). Indomethacin was the first drug used, but this drug has been associated with several side effects, including renal damage.[8] Ibuprofen, which is a cyclooxygenase-2 inhibitor, was subsequently introduced into clinical practice and the reduced vasoconstrictor effect leads to less impairment of renal function.[9,10] As a result of some restrictions on the administration of ibuprofen in premature infants, such as the presence of pulmonary hypertension or hyperbilirubinemia,[6] acetaminophen became an alternative PDA treatment drug. Acetaminophen prevents the conversion of arachidonic acid to PGE2 via inhibition of the peroxidase segment of prostaglandin synthase, which leads to fibrosis and anatomical ductal closure.[11–13]

Acetaminophen has a better safety profile than ibuprofen; however, the effect in the achievement of PDA closure is similar.[14] This randomized clinical trial was conducted to determine the efficacy and safety of the synchronous use of acetaminophen and ibuprofen for the treatment of PDA in premature neonates.

METHODS

The study is registered with the Iranian Registry of Clinical Trials (no: IRCT201171116037503N2) and conducted according to the appropriate principles. After receiving approval of the study protocol from the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1396.72), informed consent was obtained from the parents of the newborns.

This randomized, controlled trial study was conducted with neonates of fewer than 37 gestational weeks who were admitted to the neonatal intensive care units of 2 hospitals (Nemazee Hospital and Hafez Hospital) affiliated with the Shiraz University of Medical Science between March 2016 and March 2017. All premature infants with signs of PDA, such as tachypnea, decreased oxygen saturation, and increasing respiratory support aged up to 14 days were selected for echocardiography. A diagnosis of hemodynamically significant PDA was made by a pediatric cardiologist according to the clinical signs and the result of the echocardiography examination.

Echocardiography

The following criteria were considered to determine hemodynamically significant PDA using M-mode, as stated in the literature: an enlargement of the left atrium with a ratio of the left atrium to the aortic valve of ≥1.5, retrograde diastolic flow in the superior mesenteric artery or in the anterior cerebral artery, a moderate or large ductus arteriosus diameter of ≥1.5 mm at the narrowest point, and an unrestrictive pulsatile transductal flow.[15] In the event the neonatologist held a clinical suspicion of PDA, the diagnosis was confirmed with echocardiography within 24 hours.

Inclusion and exclusion criteria

Any premature newborn with a bleeding tendency, such as bleeding from an endotracheal tube, gastrointestinal bleeding, or oozing from puncture sites, or an IVH grade 3–4 was excluded from the study. Prema-

ture neonates with congenital heart disease were also excluded. Furthermore, patients with a platelet count of <50,000 mm^3, urine output of <1 mL/kg/hour, serum creatinine level of >1.5 mg/dL, proven sepsis, and elevated liver enzyme levels were also excluded.

Demographic data, including gestational age at birth, type of delivery, sex, age, and Apgar score at the fifth minute after birth were collected from the medical chart of each patient. The weight of the neonates was also measured and recorded.

Intervention

Premature neonates with significant PDA were divided into 3 subgroups based on simple randomization of the subjects using a random number table. The assigned intervention was initiated within 24 hours after diagnosis of significant PDA. The first group received intravenous acetaminophen 15 mg/kg every 6 hours for 3 days, based on a previously reported regimen[6] and the second group received oral ibuprofen at the standard dose of 10 mg/kg for the first 24 hours followed by 5 mg/kg for the next 48 hours.[16] The third group simultaneously received intravenous acetaminophen 15 mg/kg every 6 hours for 3 days and an initial oral ibuprofen dose of 10 mg/kg for 24 hours followed by 5 mg/ kg for 48 hours.

Echocardiography was repeated by the same pediatric cardiologist within 24 hours of completing the course of treatment, and complete closure of PDA was defined as a response to treatment. A determination of nonclosure of PDA after the echocardiography evaluation prompted a repeat second course of the assigned treatment. The second course was initiated within 24 hours of the echocardiography result. Primary closure was defined as the closure of ductus arteriosus after the first 3-day intervention treatment and secondary closure was defined as closure of ductus arteriosus after 2 courses of 3-day interventional drug use.

The safety of the regimens was assessed with daily measurement of blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, and platelet values. Drug treatment was terminated with the occurrence of a bleeding tendency, IVH grade 3–4, renal or liver dysfunction, NEC, or intestinal perforation. Adverse events were defined as those occurring up to 1 week after administration of the drug. The use of other NSAIDs was not permitted for any purpose during the study.

The study results were reported as mean±SD for the quantitative variables and percentages for the categorical variables. The groups were compared using the Student's t-test or the Mann-Whitney U test for the continuous variables and a chi-square test (or Fisher's exact test, if required) for the categorical variables. The trends of the changes in the study variables were examined using an analysis of variance trend test. A p value of <0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

The parents of 224 of 260 eligible premature newborns with PDA agreed to participate in this study. Among the patients, 25 were excluded due to congenital heart disease, thrombocytopenia, a congenital anomaly, or IVH, and 19 patients died before beginning the intervention. In all, 180 premature newborns with hemodynamically significant PDA were randomly assigned to the 3 subgroups. A total of 154 patients completed the study: 67 patients (45 female, 22 male) in the first group, which was treated with acetaminophen; 68 patients (32 female, 36 male) in the second group, which received ibuprofen; and 19 patients (11 female, 8 male) in the third group, the combination acetaminophen and ibuprofen group. The study flowchart is presented in Figure 1. No significant differences were observed between the 3 treatment groups in terms of sex distribution (p=0.06).

The demographic data and laboratory results of the treatment groups are summarized in Table 1; the Kruskal Wallis test revealed significant differences between the groups in the gestational age and the Apgar score recorded at the fifth minute. The number of cesarean section births among the 154 premature newborns with PDA was 54 (35.0%) in the first group, 50 (32.5%) in the second group, and 18 (11.7%) in the third group. There were no significant differences between the 3 treatment groups related to the type of delivery (p=0.21).

After the first course of therapy, there was no significant difference in response between the 3 treatment groups (Table 2, Fig. 2). After the second course of drugs, the closure rate was 43.7% (7/16 patients) in the acetaminophen group, 62.5% (10/16 patients)

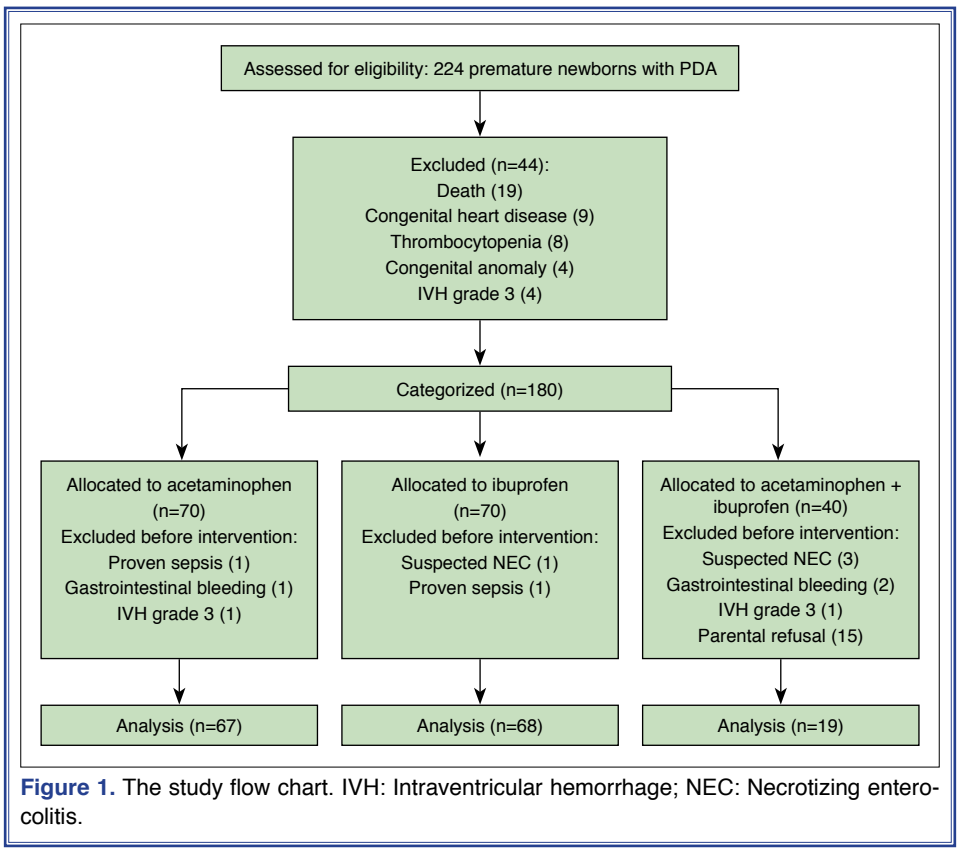

Figure 1. The study flow chart. IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis.

in the ibuprofen group, and 100% (4/4 patients) in the acetaminophen+ibuprofen group (p=0.26). The total closure rate after 2 courses of drugs was 86.5% in the acetaminophen patients, 91.1% in the ibuprofen patients, and 100% in the acetaminophen+ibuprofen patients (p=0.41) (Table 2).

The response to treatment was compared between the 3 groups by age, sex, and weight, and only a weight over 1500 g was statistically significant (p=0.03) (Table 3).

The safety of the 3 treatment groups was assessed by comparing the baseline and post-treatment liver

Table 1. Baseline demographic data and laboratory results of the study groups

Characteristics	Acetaminophen group (n=67)	Ibuprofen group (n=68)	Acetaminophen+ibuprofen group (n=19)	*p*-value
	Mean±SD	Mean±SD	Mean±SD	
Gestational age (weeks)	30.98±2.90	31.14±2.35	30.36±2.39	0.06
Age (days)	5.33±3.99	5.44±2.37	8.52±5.90	0.17
Weight (g)	1334.0±512.91	1353.59±333.15	1264.74±509.54	0.66
Apgar score	7.89±1.34	8.81±1.21	7.53±1.47	<0.01
Alanine aminotransferase (IU/L)	13.45±3.12	10.00±2.75	17.00±5.87	0.94
Aspartate aminotransferase (IU/L)	44.33±5.88	35.28±2.75	35.89±4.83	0.59
Bilirubin (mg/dL)	6.02±0.47	7.26±0.64	6.70±0.53	0.25
Blood urea nitrogen (mg/dL)	19.70±1.93	13.07±2.10	22.42±2.21	0.06
Creatinine (mg%)	0.69±0.04	1.00±0.61	0.47±0.05	0.22
Platelet (10^3/mm^3)	195.70±10.20	221.21±10.40	198.47±11.20	0.40

Table 2. Efficacy of the treatments to provide occlusion of PDA in the premature newborns studied

Closure rate of PDA	Acetaminophen (n=67)	Ibuprofen (n=68)	Acetaminophen+ibuprofen (n=19)	p-value
Primary closure rate, n (%)	51 (76.1)	52 (76.4)	15 (78.9)	0.97
Secondary closure rate, n (%)	7 (10.4)	10 (14.7)	4 (21.1)	0.30
Total closure rate, n (%)	58 (86.5)	62 (91.1)	19 (100)	0.41

PDA: Patent ductus arteriosus.

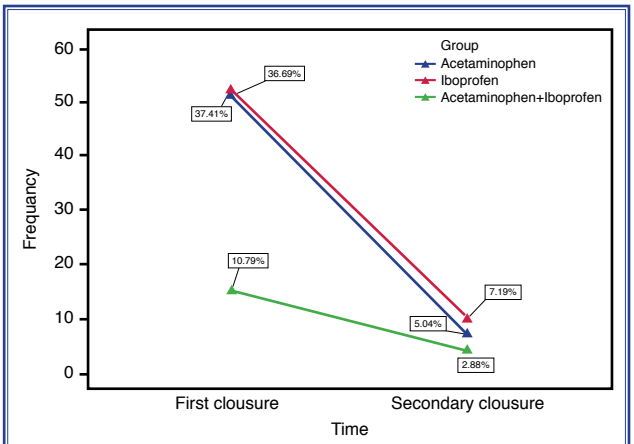

Figure 2. Patent ductus arteriosus closure rate in the premature infants studied.

and renal enzyme levels as well as the platelet count. The data revealed no significant differences in the results of the laboratory findings before and after the application of the 3 treatment modalities other than the platelet value. The increase in the platelet count was greater in the newborns treated with acetaminophen+ibuprofen (311.1±30.4/mm^3) compared with acetaminophen (226.4±11.1/mm^3) and ibuprofen (245.0±28.3/mm^3) (p=0.008). There was no occurrence of bleeding tendency, BPD, or NEC after treatment in any group.

DISCUSSION

Acetaminophen and ibuprofen have emerged as treatment options for hemodynamically significant PDA; however, some neonates may not respond to this treatment. The results of this study indicated that the synchronous use of acetaminophen and ibuprofen was effective in prompting closure of the ductus arteriosus, and the treatment was more successful in the second course than the use of single drugs. No adverse events attributable to any of the 3 types of therapy used were detected.

In this study, the overall PDA closure response rate in premature infants to acetaminophen alone was 86.5%. Numerous studies have shown that acetaminophen is efficacious in promoting the closure of the ductus arteriosus. In 2011, Hammerman et al.[17] were the first to report the effect of acetaminophen in achieving closure of a patent ductus arteriosus. Consistent with our results, Dang et al.[14] and Oncel et al.[18] also observed that respectively, 81.2% and 72.5% of premature infants developed successful closure of the ductus arteriosus after acetaminophen therapy. In recent years, a 91% rate of total PDA closure was reported by Bagheri et al.[19] in our area (Iran).

Ibuprofen is a nonselective cyclooxygenase inhibitor; ductal closure of ductus arteriosus using ibuprofen alone was determined to be 76.4% after the first course and 14.7% after the second course in this study. Varvarigou et al.[20] were the first to publish a report of the effectiveness of ibuprofen for closure of a patent ductus arteriosus in human preterm infants and the results of other studies support the drug's efficacy in this purpose.[21,22] Similar to our study findings, the ductus arteriosus closure rate was determined to be 71% and 11.7% after the first and the second course of ibuprofen, respectively, in a study of Turkish neonates.[23]

A Cochrane Review concluded that the successful ductal closure rate for acetaminophen was similar to that of ibuprofen in some clinical trials.[24] In this study, the total rate of occlusion was lower in the acetaminophen group (not statistically different). Our study used a short course of 3 days of acetaminophen, while some authors have applied a long course of acetaminophen (>3 days) and seen a greater rate of ductal closure.[24] A low Apgar score at 5 minutes after birth is a risk factor for PDA in very low birthweight infants, and a higher response

Table 3. Comparison of the response to treatment in the 3 study groups by age, sex, weight, and gestational age

Characteristic	Response	Acetaminophen (n=67)	Ibuprofen (n=68)	Acetaminophen+ibuprofen (n=19)	*p*
Age (days), n (%)					
1–3	NO PDA	19 (28.5)	24 (35.3)	2 (10.5)	0.49
	PDA	7 (10.4)	5 (7.3)	1 (5.3)	
4–7	NO PDA	21 (31.3)	26 (38.2)	10 (52.6)	0.45
	PDA	10 (14.9)	8 (11.8)	1 (5.3)	
>7	NO PDA	8 (11.9)	4 (5.9)	3 (15.8)	0.14
	PDA	2 (3.0)	1 (1.5)	2 (10.5)	
Sex, n (%)					
Male	NO PDA	18 (26.9)	30 (44.1)	6 (31.6)	0.79
	PDA	4 (6.0)	6 (8.8)	2 (10.5)	
Female	NO PDA	35 (52.2)	24 (35.3)	9 (47.4)	1.00
	PDA	10 (14.9)	8 (11.8)	2 (10.5)	
Weight (g), n (%)					
<1000	NO PDA	18 (26.8)	7 (10.3)	6 (31.6)	0.49
	PDA	5 (7.5)	5 (7.4)	2 (10.5)	
1000–1500	NO PDA	20 (29.8)	28 (41.2)	6 (31.6)	0.64
	PDA	4 (5.9)	8 (11.7)	0	
>1500	NO PDA	15 (22.5)	19 (27.9)	3 (15.8)	0.03
	PDA	5 (7.5)	1 (1.5)	2 (10.5)	
Gestational age (weeks), n (%)					
<30	NO PDA	29 (43.3)	11 (16.2)	7 (36.9)	0.72
	PDA	8 (11.9)	5 (7.3)	1 (5.3)	
30–34	NO PDA	17 (25.5)	36 (53.0)	8 (42.0)	0.65
	PDA	4 (5.9)	7 (10.3)	3 (15.8)	
>34	NO PDA	7 (10.4)	7 (10.3)	0	1.00
	PDA	2 (3.0)	2 (2.9)	0	

PDA: Patent ductus arteriosus.

in the ibuprofen group might be due to a high Apgar score at the fifth minute in this group of our study population.[25]

To the best of our knowledge, there is only 1 previous study examining the addition of acetaminophen to ibuprofen to encourage closure of the ductus arteriosus in premature infants. Hochwald et al.[26] compared the PDA closure rate in patients treated with ibuprofen+paracetamol versus ibuprofen+placebo and observed that there was no greater trend toward closure with the combination therapy. The present study results demonstrated a beneficial effect for ibuprofen+paracetamol in a closure rate of 100% versus 86.5% in the acetaminophen group and 91.1% in the ibuprofen group, but the rates were not statistically significantly different.

Newborns weighing >1500 g had a higher rate of closure in all of the treatment groups in this study. It appears that greater birth weight can be a predictive factor for a better response to pharmacologic treatment of PDA closure. Both acetaminophen and ibuprofen can have adverse effects, such as renal damage, liver dysfunction, and bleeding tendency; however, our study found no complications related to the drugs administered in any of the 3 groups.

Study limitations

The major limitation of our study is the lack of a con-

trol group. Without a control group, this study cannot differentiate between spontaneous closure during the treatment period and the effect on the PDA of the 3 interventions studied. Parent refusal to participate in the combination group was an important cause of the small sample size in this study group. Furthermore, consideration of the impact of some risk factors, including antenatal corticosteroids and surfactant use, on response to treatment is recommended in further research.

Conclusion

The concomitant use of acetaminophen and ibuprofen can be an effective option to achieve PDA closure. Additional studies with a larger sample size are recommended in order to confirm the results.

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