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ORIGINAL ARTICLE

Comparison of Ibuprofen Protocols in the Pharmacological Treatment of Patent Ductus Arteriosus

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Abstract

Introduction: Ibuprofen (IBU) is an effective agent for the pharmacological treatment of patent ductus arteriosus (PDA) in premature infants. In this study, we compared the efficacy and complications of intravenous bolus therapy (IVBT) and continuous intravenous infusion therapy (CIVIT) for the treatment of PDA.

Methods: The study was conducted with 64 preterm infants in neonatal intensive care unit with gestational age <34 weeks between 2015 and 2018. Demographic characteristics, clinical findings, complications, and response to treatment were evaluated.

Results: IBU treatment with a standard dose (10/5/5 mg/kg) was given as IVBT in 48.4% (n=31) of the patients and as CIVIT 51.6% (n=33) of the patients. The efficacy and the side effects of the treatment modalities were compared. In CIVIT group, feeding intolerance was found in 6 patients (18.2%) and none of them had Stage 3 necrotizing enterocolitis (NEC). In the IVBT group, 15 patients (48.4%) had feeding intolerance and 3 patients (9.7%) had Stage 3 NEC. Surgical ligation was needed in 3 (9.7%) patients who received IVBT. There was no need for surgical ligation in patients who received CIVIT. No significant difference was found between two groups in terms of mortality, hospital stay, periventricular hemorrhage, and side effects such as oliguria, renal insufficiency, hyponatremia, and bleeding diathesis.

Discussion and Conclusion: When IBU is used as CIVIT for the pharmacological treatment of PDA, we found that the risk of developing feeding intolerance and NEC is less than IVBT. These results should be studied with larger sample sizes.

Keywords: Continuous intravenous infusion therapy; ibuprofen; intravenous bolus therapy; patent ductus arteriosus.

The pulmonary artery and aortic arch are connected through a vascular shunt, called the ductus arteriosus, in fetal life. Although ductus arteriosus closes spontaneously a few hours after birth in term babies, it may be delayed in premature babies[1,2]. Patent ductus arteriosus (PDA) affects approximately 20% of premature babies born before particularly the 32nd week of gestation (gestational week [GW]). The incidence of PDA is inversely proportional to birth weight (BW) and GW. While the frequency of PDA is 30% in babies with a BW below 1500 g, this rate is 40% in babies with a weight between 751 and 1000 g and 50% in babies between 501 and 750 g. Mortality rates are higher in premature babies with left-to-right shunt due to PDA. In addition, respiratory failure due to respiratory distress syndrome (RDS) is more severe and the frequency of complications due to prematurity such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC) increases. For these reasons, PDA should be closed before a significant left-to-right shunt develops[2,3].

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Today, the treatment applied for PDA closure has two steps. First of all, pharmacological closure is tried with non-steroidal anti-inflammatory drugs. If this treatment fails, surgical ligation is performed. While the ductus can be closed with pharmacological treatment in approximately 80% of premature babies with PDA, approximately 6.5% of the patients require surgical ligation. Ibuprofen (IBU) is a cyclooxygenase (COX) inhibitor. It is a drug with similar efficacy with indomethacin used for the same purpose and has become a preferred treatment in many neonatal intensive care units due to its less negative effects on renal functions and the lower incidence of NEC complications resulting from peripheral vasoconstriction and poor organ perfusion[4-7]. In various studies, closure rates of PDA with the use of IBU have been determined between 57% and 89%. However, these drugs have serious side effects such as gastrointestinal perforation, acute renal failure as a result of impaired renal function, and bleeding diathesis due to decreased platelet count. Although IBU appears to be a safe drug with few side effects compared to indomethacin, it has a failure rate of 30% in PDA closure[6]. Although pharmacological closure treatment is often the preferred method of treatment due to the risks associated with surgery and anesthesia, the approach to PDA closure is still controversial. In a study conducted by Lago et al.[8] it was shown that administering IBU by 24 h infusion is more successful in closing the PDA than by intravenous bolus. In the same study, it was found that the need for surgical treatment and the risk of NEC were lower in patients who received infusion therapy, than those who received bolus therapy.

In this study, the effects and side effects of intravenous bolus therapy (IVBT) and continuous intravenous infusion therapy (CIVIT) in premature babies born before 34 GW and with pharmacological closure indication for PDA were compared.

Materials and Methods

Study Plan

This study was carried out retrospectively with preterm patients born before 34 GW who were hospitalized in the neonatal intensive care unit between January 2015 and January 2018.

The study protocol was approved by the Ethics Committee of our university hospital. Written consent was obtained from each patient's mother or father that they agreed to participate in the study.

Study Groups

In this study, 64 patients who were born before the 34th GW and who were found to have hemodynamically significant PDA in echocardiography (ECHO) were included. IBU was administered to 31 of these patients in the form of IVBT and to 33 patients as CIVIT. Patients with congenital anomalies were excluded from the study.

Transthoracic ECHO was performed by an experienced pediatric cardiologist at postnatal 48th-72nd h to all patients. The diagnosis of hemodynamically significant PDA was made according to the following criteria: (1) The ductus diameter being more than 1.6 mm and (2) the left atrium width/aortic root ratio being greater than 1.4. In patients with hemodynamically significant PDA in need of medical treatment, IBU treatment was administered as IVBT for 15 min for those who were hospitalized and treated between 2015 and 2016, and as CIVIT for 24 h between 2017 and 2018. IBU was administered in three doses as a course, first cycle being 10/5/5 mg/kg/day, second cycle as 14/7/7 mg/kg/day, and third cycle as 18/9/9 mg/kg/day. The ductus diameter and left atrium width/aortic root ratio were followed by daily ECHO. PDA was closed with surgical ligation in cases where the administration of IBU was contraindicated or in cases where treatment was unsuccessful.

Variables Examined in the Study

In addition to variables such as gender, GW, BW, type of delivery, multiple pregnancy, RDS, need for surfactant, development of BPD, need for ligation, the effects of both IBU protocols on serum creatinine level, platelet count in complete blood count and hourly urine output rate, and their effects of NEC development, IVH development, hospital stay, and mortality, were compared. GW was calculated based on mother's last menstrual date or Ballard score.

The daily urine output of the patients in both groups was calculated on an hourly basis. Daily serum creatinine and platelet count in complete blood count before and after IBU administration were monitored. IBU treatment of patients with serum creatinine level above 1.2 mg/dL and platelet count below 100.000/uL was terminated and these patients were excluded from the study.

In the follow-up of the patients, according to the protocol of our unit, the presence of IVH was investigated by serial cranial ultrasound sonography in the coronal and sagittal sections from the anterior fontanelle with a 7.5 MHz transducer in the first 24 h, on the 3rd day and at the end of the 1st week, or in suspicious cases.

NEC diagnosis was made with clinical and radiological

findings. It was divided into three phases according to the Modified Bell's Staging Criteria. Nutritional intolerance was evaluated as a separate finding. Gastric residual volume of more than 50%, vomiting, or abdominal distension (increase of abdominal circumference more than 2 cm) were defined as feeding intolerance. Cases with suspected NEC were followed up with direct abdominal X-ray images, obtained in a standing position taken serially at 12 h intervals. Patients with Stage 3 NEC were accepted as a complication of IBU treatment.

Statistical Analysis

Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) program was used for statistical analysis. While evaluating the data of the study, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, and ratio), Shapiro-Wilk test was used for the compliance of the data to normal distribution. Student's t-test was used for intergroup comparisons of normally distributed variables, and Mann–Whitney U-test was used for intergroup comparisons of variables that did not show normal distribution. The repeated measures test was used for in-group comparisons, and the Bonferroni test was used for *post hoc* comparisons. Pearson's Chi-square test and Fisher's exact test were used to compare qualitative data. Results were evaluated at 95% confidence interval, at the significance level of $p<0.05$.

Results

This study was conducted with 64 babies hospitalized in Bahçeşehir University Göztepe Medicalpark Hospital neonatal intensive care unit between January 2015 and January 2018. The demographic characteristics of the patients are given in Table 1. While IVBT was applied to 48.4% (n=31) of IBU cases, CIVIT treatment was applied to 51.6% (n=33) of them.

No statistically significant difference was found between mean GW according to IBU treatment types ($p>0.05$). There was no statistically significant difference in gender distributions, type of delivery, and length of hospital stay. The median BW in the CIVIT group tended to be higher, but was not statistically significant ($p>0.05$).

No statistically significant difference was found in both groups in terms of RDS frequency, need for surfactant treatment, development of BPD, number of IBU treatment, and ligation treatment rates ($p>0.05$) (Table 2). No statistically significant difference was found in both groups in serum creatinine values checked on the 1st, 2nd, and 3rd days of

Table 1. Evaluation of demographic characteristics according to IBU treatment groups

	Total	IBU treatment type	
		IVBT (n=31)	CIVIT (n=33)
GW			
Min-max (median)	24-34 (29)	24-34 (28)	25-33 (29)
Mean±SD	28.66±2.73	28.10±3.15	29.18±2.20
Gender			
Female	23 (35.9)	10 (32.3)	13 (39.4)
Male	41 (64.1)	21 (67.7)	20 (60.6)
Type of delivery			
NSD	6 (9.4)	4 (12.9)	2 (6.1)
C/S	58 (90.6)	27 (87.1)	31 (93.9)
BW			
Min-max (median)	630-2960 (1180)	630-2960 (1050)	705-1950 (1310)
Mean±SD	1211.78±429.42	1105.13±477.54	1311.97±357.60
Hospital stay (day)			
Min-max (median)	21-276 (39)	21-185 (40)	22-276 (38)
Mean±SD	54.67±41.97	55.74±37.29	53.67±46.50
Multiple pregnancy			
Present	30 (46.9)	17 (54.8)	13 (39.4)
Absent	34 (53.1)	14 (45.2)	20 (60.6)

IVBT: Intravenous bolus therapy; CIVIT: Continuous intravenous infusion therapy; GW: Gestational week; BW: Birth weight; IBU: Ibuprofen; NSD: Normal spontaneous delivery.

Table 2. Evaluation of RDS, surfactant need, development of BPD, number of IBU cycles, and need for surgical ligation treatment according to treatment groups

	Total	IBU treatment type	
		IVBT (n=31)	CIVIT (n=33)
RDS	62 (96.9)	30 (96.8)	32 (97.0)
Surfactant need	55 (85.9)	26 (83.9)	29 (87.9)
Development of BPD	45 (70.3)	21 (67.7)	24 (72.7)
Number of IBU cycles			
1 cycle	46 (71.9)	22 (71.0)	24 (72.7)
2 cycle	18 (28.1)	9 (29.0)	9 (27.3)
Ligation need	3 (4.7)	3 (9.7)	0

[c]: Mann–Whitney U-test; [d]: Fisher's exact test. IVBT: Intravenous bolus therapy; CIVIT: Continuous intravenous infusion therapy; RDS: Respiratory distress syndrome; BPD: Bronchopulmonary dysplasia; IBU: Ibuprofen.

IBU treatment and following the last dose (p>0.05). There was no statistically significant difference in the changes between the creatinine measurements in the follow-up of the patients who received IVBT or CIVIT (p>0.05) (Table 3).

No statistically significant difference was found in platelet counts in the total blood count taken on the 1st, 2nd, and 3rd days of IBU treatment and after the last dose, compared according to IBU treatment types (p>0.05) (Table 4).

There was no statistically significant difference in the 24 h urine output follow-up of the patients, on the 1st, 2nd, and 3rd days of IBU treatment, and urine output rate after the last dose, compared according to the IBU treatment types (p>0.05) (Table 5). The changes in the direction of decrease in the second, third, and last measurements in the urine output rates of the patients who received IVBT, compared to the 1st day, were found to be statistically significant (p=0.006; p=0.041; and p=0.049, respectively). There was no statistically significant difference in the changes between urine output rates in CIVIT receivers (p>0.05) (Fig. 1).

A statistically significant difference was found between the groups in terms of nutritional intolerance (p<0.05), and the feeding intolerance in the IVBT group was 2.5 times higher than in the CIVIT group. In addition, development of NEC requiring surgical treatment was seen in three patients who received IVBT, but was not detected in the CIVIT group (Fig. 2). There was no significant difference between the groups in terms of IVH frequency and length of hospital stay (p>0.05). In our study group, the mortality rate was 17.2% (n=11), and mortality was seen in 7 patients (22.6%) in the IVBT group and in 4 patients (12.1%) in the CIVIT group. No statistically significant difference was found between these rates according to IBU treatment types (p>0.05) (Table 6).

Table 3. Evaluation of serum creatinine measurements according to treatment groups

Creatinine	IBU treatment type	
	IVBT (n=31)	CIVIT (n=33)
1st day[a]	0.813±0.16	0.775±0.13
2nd day[b]	0.824±0.18	0.765±0.17
3rd day[c]	0.818±0.19	0.76±0.18
Last measurement[d]	0.819±0.22	0.779±0.2
[e]*P*	0.970	0.881

[a]: Student's t-test; [b]: Pearson correlation analysis; [c]: Mann–Whitney U-test; [d]: Fisher's exact test; [e]: Repeated measures test. IVBT: Intravenous bolus therapy; CIVIT: Continuous intravenous infusion therapy; IBU: Ibuprofen

Table 4. Evaluation of platelet count according to treatment groups

Platelet count	IBU treatment type	
	IVBT (n=31)	CIVIT (n=33)
1st day[a]	221.354±49.650	204.272±73.669
2nd day[b]	214.354±60.629	207.121±96.477
3rd day[c]	196.354±71.679	212.424±64.244
Last measurement[d]	216.064±96.243	207.060±66.041
[e]*P*	0.178	0.735

[a]: Student's t-test; [b]: Pearson correlation analysis; [c]: Mann–Whitney U-test; [d]: Fisher's exact test; e: Repeated measures test. IVBT: Intravenous bolus therapy; CIVIT: Continuous intravenous infusion therapy; IBU: Ibuprofen

Table 5. Evaluation of hourly urine output rates (ml/kg/hour) according to treatment groups

Urine output rate	IBU treatment type	
	IVBT (n=31)	CIVIT (n=33)
1st day[a]	5.10±1.66	4.88±1.60
2nd day[b]	4.21±1.39	4.79±1.54
3rd day[c]	4.36±1.58	4.57±1.10
Last measurement[d]	4.28±1.60	4.55±1.36
[e]*P*	0.003**	0.748
Post hoc Bonferroni test	A>B; A>C; A>D	-

[a]: Student's t-test; [b]: Pearson correlation analysis; [c]: Mann–Whitney U-test; [d]: Fisher's exact test; [e]: Repeated measures test; **p<0.01. IVBT: Intravenous bolus therapy; CIVIT: Continuous intravenous infusion therapy; IBU: Ibuprofen.

Discussion

In this study, no statistically significant difference was found between IVBT and CIVIT treatments in terms of efficacy and mortality in PDA closure. In addition, no statistically significant difference was found between the two groups in terms of short-term complications such as IVH

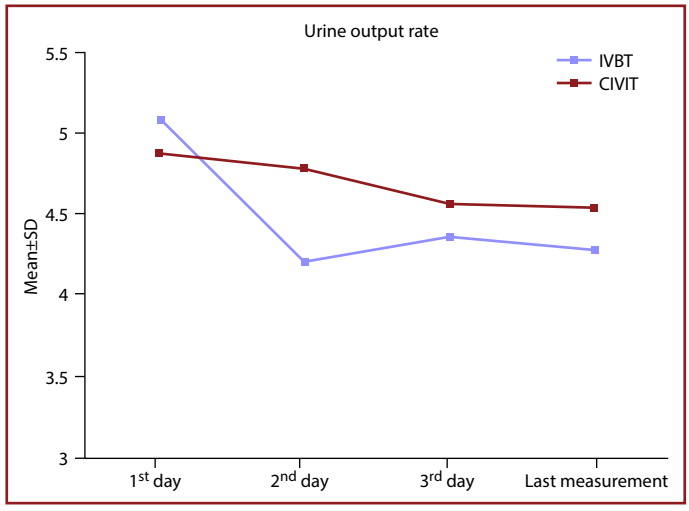

Figure 1. Distribution of urine output rates according to treatment groups.

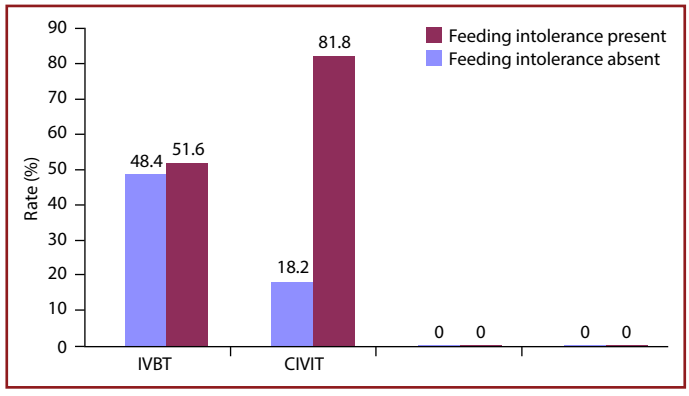

Figure 2. Distribution of feeding intolerance development by treatment groups.

and long-term complications such as BPD. Nutritional intolerance was detected 2.5 times more in the group receiving IVBT, than in the group receiving CIVIT. In the IVBT group, three patients developed Stage 3 NEC. This finding should be reexamined by conducting studies with larger cases.

Similar changes were found in both groups in parameters such as hourly urine output rate, serum creatinine level, and platelet count in complete blood count followed during IBU treatment, and were found to be statistically not significant.

Although the IBU treatment dose in pharmacological closure of PDA varies according to plasma half-life, clearance, and postnatal age, the standard dose to be given is not clear. Desfrere et al.[9] showed that high doses such as 20/10/10 mg/kg/day are more effective in PDA closure in premature babies <27 GW of age. In the study conducted by Hirt et al.[10] with 66 newborns diagnosed with PDA and treated with pharmacological PDA closure treatment, the 24 h IBU infusion treatment was reported to be more effective when administered with a dose of 10/5/5 mg/kg/day in preterm babies in their first 70 h after birth, with a dose of 14/7/7 mg/kg/day in their 70th-108th h, and with a dose of 18/9/9 mg/kg/day in their 108th-180th h. Dani et al.[11], on the other hand, reported that in the first 12-24 h of life, doubling the IBU dose (20/10/10 mg/kg/day) or reducing the interval between two infusions to 12 and 18 h contributed to the closure of PDA, but had more renal side effects. In our study, the diagnosis of PDA was made in our patients 48-72 h of life, and in patients with hemodynamically significant PDA, 10/5/5 mg/kg/day IBU treatment was initiated as the first course immediately after the diagnosis was made. PDA was evaluated with daily ECHO follow-up, and higher doses of IBU were administered in the second cycle (14/7/7 mg/kg/day) and in the third cycle (18/9/9 mg/kg/day) to our patients whose PDA did not close and who needed additional cure.

Table 6. Evaluation of complications and mortality according to treatment groups

	Total	IBU treatment type	
		IVBT (n=31)	CIVIT (n=33)
Feeding intolerance			
Present	21 (32.8)	15 (48.4)	6 (18.2)
Absent	43 (67.2)	16 (51.6)	27 (81.8)
IVH			
Present	24 (37.5)	13 (41.9)	11 (33.3)
Absent	40 (62.5)	18 (58.1)	22 (58.1)
Hospital stay (day)			
Min-max (median)	21-276 (39)	21-185 (40)	22-276 (38)
Mean±Ss	54.67±41.97	55.74±37.29	53.67±46.50
Mortality			
Alive	53 (82.8)	24 (77.4)	29 (87.9)
Ex	11 (17.2)	7 (22.6)	4 (12.1)

[b]: Pearson correlation analysis; [c]: Mann–Whitney U-test; *p<0.05. IVBT: Intravenous bolus therapy; CIVIT: Continuous intravenous infusion therapy; IVH: Intraventricular hemorrhage; IBU: Ibuprofen.

In recent years, some studies have been conducted on whether IBU treatment can be administered intravenously or orally, and in most of the studies, IBU was given as an intravenous bolus. Studies comparing the efficacy and side effects of giving IBU as 24 h infusion are very few. In a study conducted by Lago et al.[8] it was reported that the application of IBU in very low BW infants was more effective than IVBT, and NEC complications and surgical ligation rates were less in patients. In this study, pharmacological PDA closure was found to be 64% in the IV bolus group and 83% in the continuous infusion group. In the same study,

although no clear data were mentioned for the appropriate plasma IBU concentration required for PDA closure, they showed that sufficient concentration rate was reached with continuous infusion.

IBU is a COX inhibitor and can cause renal side effects such as oliguria or elevated serum creatinine levels due to transient prostaglandin deficiency, especially in immature kidneys. This is due to the vasodilator effect of prostaglandins on afferent glomerular arterioles of glomerular filtration in the early neonatal period[6,8,12]. Vieux et al.[13] showed that the glomerular filtration rate was lower in patients with a GW of <32 and using IBU in PDA closure treatment, compared to those who did not need PDA treatment. Renal hypoperfusion and IVH may develop due to changes in blood flow changes in patients with PDA. In our study, oliguria did not develop in patients who received IVBT and CIVIT. In addition, we found no statistically significant difference in hourly urine output rate and serum creatinine levels. We did not find a statistically significant difference in terms of IVH development in patients in both groups.

The high IBU plasma levels during IVBT can lead to severe intestinal vasoconstriction and local microcirculation reduction, resulting in NEC[8]. In our study, we did not detect Stage 3 NEC in the group receiving CIVIT, although there was feeding intolerance.

Conclusion

As a result, we found no statistically significant difference in PDA closure and surgical ligation need between CIVIT and IVBT of IBU in the pharmacological closure treatment of PDA. Although our study suggests that CIVIT of IBU may reduce the risk of feeding intolerance and NEC, studies with more cases are needed to evaluate the safety of the drug.

Ethical Committee Approval: Study was approved by the Ethics Committee of Bahçeşehir University School of Medicine (20/09/2017 decision number 2017-14/02).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: Y.C., I.A., G.K.; Design: Y.C., I.A., G.K.; Data Collection or Processing: Y.C.; Analysis or Interpretation: Y.C., I.A.; Literature Search: Y.C.; Writing: Y.C.

Conflict of Interest: None declared.

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