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Effectiveness and Safety of High Dose Oral Ibuprofen versus Standard Dose for Treatment of Preterm Infants with Patent Ductus Arteriosus

Dahlia El Sebaie [1], Shaimaa Mohamed Hassan Ali [2*], Yasmeen Mansi [1], Rodina Sobhy [1], and Amira M. Sabry [1]

[1]Pediatric Department, Cairo University, [2]Neonatology Department, El Sahel Teaching Hospital, Cairo, Egypt

[*]**Corresponding author:** Shaimaa Mohamed Hassan, **E-mail:** dr.shama2612@gmail.com,
Phone: +201010761933. **Orcid:**0000-0003-0871-2021

ABSTRACT

Background: One of the most significant changes needed for the transition to extrauterine life is the ductus arteriosus (DA) closure, which is located in the fetal circulatory system between both the aortic arch and the pulmonary artery. The extended length of patent DA (PDA), that further raises premature mortality and morbidity, impairs hemodynamics. The effectiveness and tolerability of oral ibuprofen administered at regular and high doses to treat PDA were examined in this research.

Patients and Methods: The newborn Critical Care Unit at Cairo University Pediatric Hospitals received 60 preterm neonates (Gestational age<36 weeks) with clinically severe PDA during the course of 2.5 years. A randomized controlled trial was used in the investigation. They were divided into two groups at random, with the first receiving oral ibuprofen at a standard dose (10, 5, 5 mg/kg/day) and the second receiving oral ibuprofen at a high dose (20, 10, 10 mg/kg/day) for three days straight.

Results: The neonates in our experiment exhibited a considerable reduction in PDA size both before and after taking it, and no statistical considerable difference between two regimens of ibuprofen was existent. Despite the fact they stayed within the scope of normal range for age in the high-dose group, serum creatinine level rose by two to three times following ibuprofen treatment. To completely comprehend this conclusion, further study is needed. **Conclusions:** Our results show that regular-dose ibuprofen for PDA closure is just as effective as high-dose ibuprofen with fewer side effects.

Keywords: Preterm Neonate; High Dose Oral Ibuprofen; Ductus Arteriosus.

INTRODUCTION

Normal term delivery causes the ductus arteriosus to spontaneously shut; in preterm neonates, it often doesn't. A left-to-right shunt triggered by the disease known as patent ductus arteriosus (PDA) can potentially lead to hemodynamic abnormalities such pulmonary fluid overload as well as a decrease in systemic circulation. This has been linked to chronic lung illness, necrotizing entero-colitis (NEC), and extended ventilation. PDA may be managed medically or surgically by ligation. There is now a global discussion on the ideal PDA drug management approach [(1)].

It is crucial to identify between such a clinically significant or non-significant PDA before deciding on a course of treatment. The preterm newborns' respiratory state is made worse by the hemodynamically severe PDA by increasing the infants' previously manageable ventilator support and oxygen requirements [(2)].

Ibuprofen, a non-steroidal anti-inflammatory medication, causes the PDA to close by blocking cyclo-oxygenase. When administered during the first three postnatal days, ibuprofen proved particularly effective in closing the ductus arteriosus [(3)]. Additionally, different research discovered that using high doses of ibuprofen (20-10-10 mg/kg/day for three days straight) is more efficient than using conventional doses (10-5-5 mg/kg/day for three days straight) while reducing the incidence of side effects [(4)].

PATIENTS AND METHODS

The newborn intensive care unit of Cairo University Pediatric Hospitals admitted 60 preterm neonates (Gestational age<36 weeks) with clinically severe PDA between March 2016 and December 2018. This research was a randomized controlled trial investigation. Neonatal patients were admitted upon parental signed informed permission.

Preterm newborns (Gestational age<36 weeks) within the first week of life must meet the inclusion criteria, as well as a pediatric cardiologist must find clinical or echocardiographic evidence of a hemodynamically severe PDA.

Significant congenital defects, a serum creatinine level of less than 1.5 mg/dl,a platelet count of less than 50,000/mm^3, and a history of bleeding tendencies are all considered exclusion factors (for example; hematuria, bloody endotracheal aspirate, bloody gastric aspirate, blood in stools, or blood oozing from puncture sites).

A comprehensive clinical examination was done both before and throughout treatment throughout the intervention, daily measurements of rate of heart, blood pressure, capillary refill time, and output of urine was taken. Blood samples for the full blood count, CRP, serum creatinine, urea, liver enzymes, bilirubin, blood cultures, chest X-ray, cranial ultrasound, and echocardiography were also included. Additionally, these tests were done before the patient began taking the medicine, every other day while it was being taken, at the conclusion of the ibuprofen administration, or as soon as a doctor deemed it necessary.

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Ethical approval:

The informed written consent to participate in the current experiment was given by the parents of each neonate. The Medical Sciences Ethical Committee of the Faculty of Medicine of Cairo University fgave its approval for this investigation. The Declaration of Helsinki, the code of ethics for human research adopted by the World Medical Association, was followed throughout the conduct of this experiment.

Statistical analysis

Data were statistically analyzed in regards of mean, standard deviation (SD), and frequency (percentages). The Mann Whitney U test was run when the data were not normally distributed and the student t test was run when they were. The definition of significant data was a probability value (p value) smaller than 0.05. Pearson correlation test was used .Mann-Whitney test used for comparing non paired data. Wilcoxon signed-rank test was used for comparing paired data before and after treatment. All statistical calculations were performed using SPSS statistics software (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) and Microsoft Excel Version 7.

RESULTS

In our investigation, table 1 shows that there were no statistically significant variations in the descriptive data of the examined neonates between the two groups of ibuprofen dosage for gestational age, birth weight, or APGAR score at 5 min.

Table (1): Descriptive data of studied neonates

		Ibuprofen dose		P value
		Group (1) Regular dose (No. = 30)	Group(2) High dose (No. =30)	
		No. (%)		
		Mean ±SD		P value
Gestational age in wks		32.93±2.47	33.03±2.48	0.876
Birth weight (kg)		1.84±0.52	1.90±0.61	0.664
APGAR at 5 min		6.46±1.2	5.8±1.4	0.061

Table 2 shows that there was a statistically significant difference in the PDA size and the measurement of pulmonary artery pressure in each group before and after the administration of ibuprofen to the neonates under study. There were no statistically significant variations in PDA closure between the two groups before and after ibuprofen treatment.

Table (2): PDA size and pulmonary artery pressure measurement before and after ibuprofen administration among both groups

	Group (1) Regular dose (No.=30)		P -value	Group (2) High dose (No.=30)		P- value
	Before Ibuprofen	After Ibuprofen		Before Ibuprofen	After Ibuprofen	
PDA size in mm	3.32±0,77	1.97 ± 1.60	**<0.001**	3.14±.0.78	2.23±1.32	**<0.001**
PAP in mm Hg	45.93±12.17	37.50±9.58	<0.001	50.03±16.09	44.46±14.2	0.017

PDA: patent ductus arteriosus , PAP: pulmonary artery pressure

There was no statistically significant difference regarding pulmonary hypertension after ibuprofen administration among both groups (Figure1).

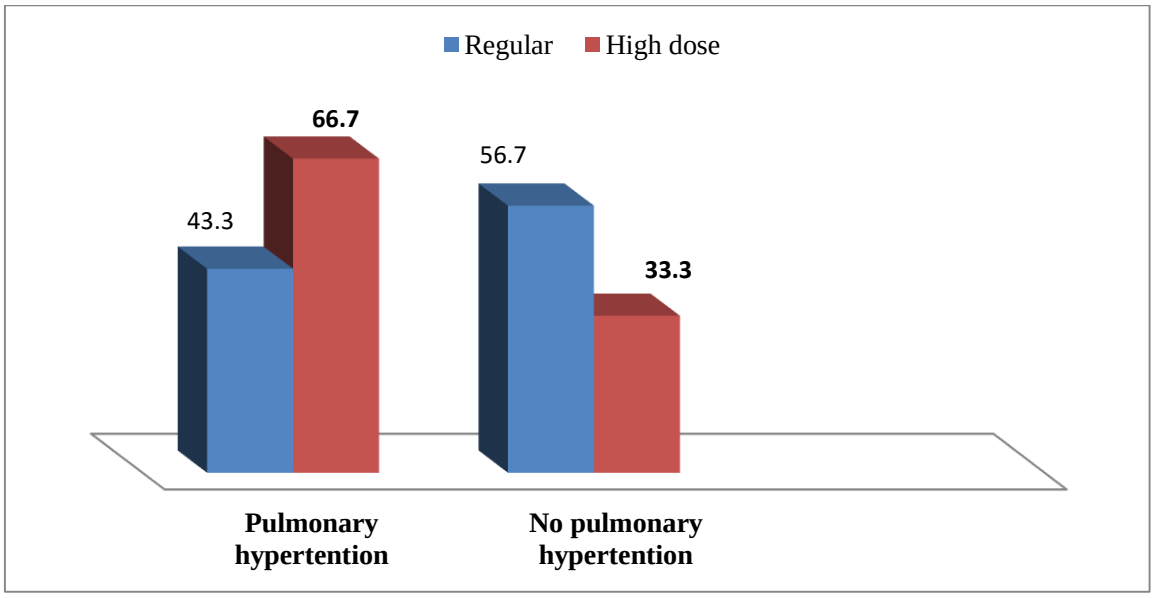

Figure (1): Pulmonary hypertension after ibuprofen administration among both groups

After receiving ibuprofen, 22 of the 60 preterm included with substantial PDA had their PDA close or become insignificant by 1.5 mm, with 13 preterm and 9 preterm in each group, with insignificant difference between both groups as demonstrated in table 3.

Table (3): PDA closure after ibuprofen administration among both groups

	Group (1) Regular dose (No. =30)		Group (2) High dose (No. =30)		P value
	Closed/ insignificant	Significant (>1.5mm)	Closed/ insignificant	Significant (>1.5mm)	
No. (%)	13(43.3%)	17 (56.7%)	9 (30%)	21 (70%)	0.284

Table (4) demonstrates that no factor influenced the PDA closure, since no statistically significant differences were existent in mean gestational age or preterm weight between closed PDA groups and non-closed groups.

Table (4): PDA closure and descriptive data of studied neonates

	PDA closed/ insignificant		PDA not closed		P value
	Mean	SD	Mean	SD	
Regular-dose Ibuprofen (No. =30)					
Gestational age in weeks	33.69	2.21	32.35	2.57	0.045
Weight in kg	1.98	0.45	1.73	0.55	0.224
High-dose Ibuprofen (No. =30)					
Gestational age in weeks	32.66	1.73	33.19	2.76	0.420
Weight in kg	1.80	0.30	1.95	0.70	0.283

There were no statistically significant correlation between PDA size before ibuprofen and different demographic data as demonstrated in table (5) .

Table (5): Correlation between PDA size before ibuprofen and age and body weight among studied neonates

PDA size before ibuprofen	r	P value
Age (week)	0.162	0.216
BW(kg)	0.018	0.891

r=Pearson correlation

There were no statistically significant changes in the other sequelae between the two groups of patients who took ibuprofen, but there have been substantial differences in the pulmonary hemorrhage and a 2-fold rise in serum creatinine level as demonstrated in table (6).

Table (6): Complications of ibuprofen treatment among studied neonates

	Ibuprofen dose		P value
	Group(1) Regular dose (No. =30)	Group(2) High dose (No. =30)	
	No (%)		
Oliguria	0	1(3.3%)	0.313
2-Fold increase in S.Cr level	0	4(13.3%)	0.038
Thrombocytopenia	5(16.7%)	10(33.3%)	0.136
Pulmonary hemorrhage	1(3.3%)	6(20.7%)	0.044
Upper GIT bleeding	8(26.7%)	6(20.0%)	0.542
NEC	4(13.3%)	0	0.038

NEC: necrotizing entero-colitis, GIT: gastrointestinal tract, S.cr: serum creatinine level

Regarding the day of life at starting ibuprofen among studied neonates, it was not significantly different between both groups of ibuprofen dose as demonstrated in table (7).

Table (7): Day of life at start of ibuprofen among studied neonates

	Group(1) (Regular dose) (No. =30)	Group(2) (High dose) (No. =30)	P value
	Mean ±SD		
Day of life at start of ibuprofen	5.4±1.86	6.2±1.98	0.061

DISCUSSION

Due to the fact that there were 22 cases with closed or insignificant PDA 1.5 mm, 13 cases (43.3 percent) in the regular dose group (1) and 9 cases (30 percent) in the high dose group, respectively; no statistically significant difference was existent in the effectiveness of closing PDA between the two groups based on our data.PDA size was 3.32 mm in group 1 before ibuprofen and 1.97 mm after ibuprofen, and 3.14 mm before and 2.23 mm after ibuprofen in group 2. PDA size in each group varied statically significantly before and after ibuprofen therapy.

In our research, group (1) started using ibuprofen on an average of 5.4 days, whereas group (2) started taking it on an average of 6.2 days.Ibuprofen is more successful than prior studies in closing the ductus arteriosus, according to **De Klerk *et al.*** [(1)], particularly when administered within the first five to six postnatal days. It was concluded that the success of ibuprofen in terms of ductus arteriosus closure in preterm neonates had been low if utilized at older postnatal ages than 6 days, even at greater dosages, in a historical cohort of 207 preterm neonates treated with basic ibuprofen dosages and particularly in comparison to a prospective cohort of 66 preterm neonates treated with postnatal age-adjusted ibuprofen dosages, between 26 and 28 weeks.

By **Dani *et al.*** [(4)] in the same issue, it was shown that the high-dose ibuprofen regimen was more effective than the regular dosage regimen in closing PDA in preterm neonates at 29 weeks of gestation. Without increasing the likelihood of unfavorable drug interactions, this was accomplished. The chance of closing PDA without meaningful adverse effects may be increased, albeit still unsatisfactory, in patients receiving a high dosage of ibuprofen (20-10-10 mg/kg/day3 consecutive days). With the present dosage regimen (10-5-5 mg/kg/dayfor 3 consecutive days), there is a low projected likelihood (30.6 percent) of newborns' PDAs closing.

Pourarian *et al.* [(5)] also noted that on the fourth day of therapy, echocardiographic assessment demonstrated 62.1 percent PDA closure in the group getting the high dosage of oral ibuprofen as opposed to 43.3 percent in the group receiving the conventional dose. Ibuprofen used in high doses was more successful in shrinking or sealing the PDA[(6)]

Furthermore, **Lu *et al.*** [(7)] discovered that a typical dosage of ibuprofen may be administered to very low birth weight (VLBW) newborns safely and effectively. Although care is advised with greater dosages in VLBW babies owing to the potential of toxicity, a higher ibuprofen dosage was linked to a better rate of closure and quicker clinical recovery. In order to treat PDA in VLBW preterm newborns, oral ibuprofen is the first line of therapy.

Regarding a 2-fold increase in serum creatinine level{0 percent – 4(13.3 percent)} respectively, there were substantial differences between the normal dosage group (1) and the high dose group (2) of ibuprofen (p = 0.038) among the neonates studied. In spite of a 2- to 3-fold increase, the serum creatinine level in the high dose group was within its normal range for its age. To completely comprehend this result, further investigation is necessary.

According to studies by **Bagnoli *et al.*[8]** on 134 preterm newborns with PDA, ibuprofen significantly impairs renal function in preterm children with a GA of 26 weeks and/or in ELBW neonates, but may be considered safe for babies with a BW >1000 g and/or GA >26 weeks.

Additionally, **Mekkhayai *et al.*[9]** found that the normal dose group saw a 2-fold increase in blood creatinine from baseline compared to the high-dose group, and that just one patient in the high-dosage group experienced oliguria (1.5 percent).

***Hirt et al.*[10]** found important effect of postnatal age on ibuprofen. Ibuprofen clearance increase in the older age of neonate.

***Oncel et al.* [11]** found that serum creatinine was higher and the incidence of acute kidney injury was higher after treatment with ibuprofen, but the difference was not statistically significant.

CONCLUSION

It was found that there was no statistically significant difference in PDA size between the normal dosage group and the high dose group, however there was between the examined neonates before and after ibuprofen treatment. Our findings show that regular-dose ibuprofen for PDA closure is just as effective as high-dose medication while having fewer negative effects.

- **Author Contributions:** Conceptualization, inspiration, original writing review, and manuscript editing the last version of the article was approved by all authors. The authors contributed to the design of the research, carried out the experiments, gathered and analyzed the data, wrote the text, and verified the accuracy of all raw data. The final text was reviewed and approved by all writers.
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