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Is Oral Ibuprofen Better than Intravenous Indomethacin for Medical Closure of the Patent Ductus Arteriosus in Preterm Infants?

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Abstract

Background: Patent Ductus Arteriosus is an open channel between the aorta and pulmonary artery. The incidence of patent ductus arteriosus (PDA) is approximately 40% in premature infants.

Objectives and Methods: To determine the effectiveness and safety of ibuprofen compared to intravenous indomethacin for closing a PDA in preterm and/or low birth weight infants. This is a case control study, retrospective review of the files of infants in control group given intravenous indomethacin, as conventional treatment: first dose of 2 mg/kg, then two doses of 0.1 mg/kg after 12 hr, 36hr respectively if the infant is either <7 days old or <1250 g, and three doses of 0.2 mg/kg if patients >7 days old or >1250 g. Infants who received oral ibuprofen in case group, as a new treatment (10 mg/kg initially followed by two doses of 5 mg/kg by interval of 24 hours) for symptomatic PDA in a neonatal intensive care unit in Pediatric and Neonatology Department, King Fahad Hospital Albaha, from January 2007 till December 2013. Only patients with isolated PDA included, while PDA associated with other congenital heart disease was excluded.

Results: A total of 104 infants as control (group 1) received IV indomethacin, and 104 pts as a case (group 2) received oral ibuprofen. Among the survivors, the closure rate was 89.4% (93/104) in the indomethacin group and 91.3% (95/104) in the ibuprofen group (p =0.443). Significantly the incidence of complications was lower in the ibuprofen group: elevated serum creatinine (14.4% versus7.7%), oliguria (19.2 % versus 9.6%), and upper gastrointestinal hemorrhage (11.5 versus 4.8%); respectively (p: 0.034, p: 0.038, and p: 0.048). The incidence of necrotizing enterocolitis was higher in the indomethacin group (5.8% versus 3.9%) but not significant (p: 0.233).

Conclusion: oral ibuprofen is as effective as intravenous indomethacin for closure of PDA and is associated with significantly less complications.

Keywords: Patent ductus arteriosus; Preterm infants; Indomethacin; Ibuprofen

Abbreviations:

IV: Intravenous; PO: Oral; PDA: Patent Ductus Arteriosus; VLBW: Very Low Birth Weight; NEC: Necrotizing Enterocolitis; UGIB: Upper Gastrointestinal Bleeding; CS: Cesarean Section; Cr: Creatinine; P value: Probability of chance; RR: Relative Risk; 95% CI: 95% Confidence Interval; 1st: First; 2nd : Second; N: Number; <: less. >: more; L: Liter; dl: Deciliter

Introduction

Patent Ductus Arteriosus is an open channel between the aorta and pulmonary artery. It should close after birth, but sometimes remains open because of the baby's premature stage of development and can lead to life-threatening complications. The incidence of patent ductus arteriosus (PDA) is approximately 40% in premature, very low birth weight (VLBW) infants (birth weight <1500 g) in our hospital, and between 30%-40% in other international studies [1,2]. The hemodynamic effects consist of disturbances in the diastolic flow of the pulmonary artery and the aorta and disturbances in the diastolic flow of the cerebral and mesenteric perfusion, which increase the risk for intraventricular hemorrhage (IVH) and gastrointestinal bleeding [3]. Before effective medical treatment more than two thirds of infants with a birth weight below 1700g required surgical closure of PDA [4,5]. Medical closure of PDA can be achieved with nonselective cyclooxygenase inhibitors, such as indomethacin and ibuprofen, which block the conversion of arachidonic acid to prostaglandins [6]. Treatment with indomethacin is associated with adverse events such as reduced renal, mesenteric, and cerebral perfusion [7,8]. Unlike indomethacin, ibuprofen has fewer effects on renal perfusion [9]. Ibuprofen has been used for closure of PDA since early 2000 [3,5,10]. IV ibuprofen is not available in most countries and is much more expensive than the oral form. The availability and lower cost of oral ibuprofen has led many physicians to use that regimen for closure of PDA [7,8,11]. Although oral ibuprofen is used widely, few randomized studies have compared its efficacy and safety with intravenous indomethacin, especially among infants with VLBW categories [12,13]. In our NICU, we are using both oral ibuprofen and IV indomethacin.The purpose of this study is to compare the efficacy and complications of intravenous indomethacin with those of oral ibuprofen in closure of PDA among infants in different VLBW categories.

The objectives of this study to determine the effectiveness and safety of oral ibuprofen compared to intravenous indomethacin for closing a PDA in preterm and/or low birth weight infants and try to know which is better ibuprofen or indomethacin for medical closure of the patent ductus.

Methods

This case control study was conducted in the neonatal intensive care unit of Pediatric Department, King Fahad Hospital Albaha, Saudi Arabia, during the period of January 2007 to December 2013. The study was approved by ethical committee. The authors have indicated they have no financial support related to this article to disclose. The inclusion criteria included preterm infants with gestational age <34 wk and a birth body weight < 1500 g. Echocardiography done within a postnatal age between 2nd and 4th day for all pts and after treatment. Patients with evidence of left-to-right shunt across the ductus arteriosus with any of the following signs: respiratory distress, increased oxygen requirements, apnea, tachycardia, bounding pulse, and widened pulse pressure, were included. Preterm infants who are more than 34 wk of gestational age, or preterm infants < 34 wk with birth body weight >1500 g, those with evidence of right-to-left shunt, infants with PDA associated with other congenital heart anomalies, and those with IVH grade 3 or 4, and pts with PDA closed spontaneously were excluded. Clinical data and information were collected from the medical records. Patients divided to two groups: group 1 considered as control group and was given intravenous indomethacin as conventional treatment, and group 2 considered as a case group was given oral ibuprofen as new modality of treatment. Medical treatment was given to preterm infants with symptomatic PDA as mentioned before. All preterm Infants in both group were subdivided into three subgroups according to birth weight: <1000 g, <1250 g, and <1500 g. Routine echocardiography screening done for all preterm infants in the 3rd or 4th day after birth by Philips echocardiography machine X50. Infants who received IV intravenous indomethacin were stratified into Group 1and was given in three doses and intervals depending on patient age; first dose of 2 mg/kg, then two doses of 0.1 mg/kg after 12 hr, 36hr respectively if the infant is either < 7 days old or < 1250 g, and three doses of 0.2 mg/kg if patients > 7 days old or > 1250 g. Infants who received oral ibuprofen as a new treatment were stratified into Group 2 as case group, 10 mg/kg initially followed by two doses of 5 mg/kg by interval of 24 hours [14] . Ibuprofen was administered through an oral-gastric tube. The outcome in our study was closure of PDA. In some cases second course given when PDA did not close. Contraindications of both medications included abnormal renal function (high serum creatinine>1.2mg/dl), and/or low platelet count. The treatment was stopped in patients when adverse effects developed or any complication included; oliguria if urine output less than 1 mL/kg/hour, elevated serum creatinine more than1.2 mg/dl (105.6 mmol/l), NEC (any stage, radiographic signs include dilated bowel loops, paucity of gas, pneumatosis intestinalis), or upper gastrointestinal bleeding (fresh blood and/or coffee-ground aspirate from the nasogastric tube, and pulmonary hemorrhage. Patient was transferred for surgical ligation if he had symptoms of heart failure or the presence of contraindication or complications to medical therapy. User's Guid to medical literature, a manual of the medical literature, a manual for evidence based clinical practice, second edition, 2008 by the American medical association was used for statistical analysis. Relative risk, Odd ratio, and 95% confidence intervals were estimated. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed on a personal computer.

Results

Variable	2007	2008	2009	2010	2011	2012	2013	Total
Total admission	442	450	446	504	510	508	641	3501
Full term	234	240	237	269	268	243	308	1799
Preterm <34 wk	208	210	209	235	242	265	333	1702
Weight <1500 g	1100 pts							
PDA diagnosed in	440 (40%). Symptomatic 302 pts (68.7%). Included 208 pts (47.3%).							

Table 1: All admitted preterm infants and pts included in the study.

Groups	Group 1 (n: 104)	Group 2 (n: 104)	p value	RR	95% CI
Gestational age mean	28.65 wk	28.5 wk	0.654		
Birth weight mean	1130.6 g	1130.5 g	0.867		
Female n (%)	56 (53.8%)	58 (55.8%)	0.55		
Male n (%)	48 (46.2%)	46 (44.2 %)	0.56		
<1000 g	32 (30.6%)	36 (34.6%)	0.422		
<1250 g n (%)	37 (35.6%)	26 (25%)	0.334		
<1500 g n (%)	35 (33.8%)	42 (40.4%)	0.288		

Treatment	IV indomethacin		Oral ibuprofen			
PDA closed	93 (89.4)%		95 (91.3)%	0.443	0.884	(0.71-1.25)
not closed	11(10.6)%		9 (8.7)%			
< 1000g	1st course	15/32 (46.9%)	16/36 (44.4%)	0.98	1.1	(0.72–1.66)
n (%)	2nd course	12/32 (37.5%)	15/36 (41.7%)			
	not closed	5/32 (15.6%)	5/36 (13.9%)			
< 1250 g	1st course	24/37 (64.9%)	18/26 (69.2%)	0.743	0.753	(0.62–1.45)
n (%)	2nd course	9/37 (24.3%)	6/26 (23.1%)			
	Not closed	4/37 (10.8%)	2/26 (7.7%)			
< 1500 g	1st course	24/35 (68.6%)	30/42 (71.4%)	0.388	0.765	(0.43–1.32)
n (%)	2nd course	9/35 (25.7%)	10/42 (23.8%)			
	Not closed	2/35 (5.7%)	2/42 (4.8%)			

Group 1: treated with intravenous indomethacin. Group 2: treated with oral ibuprofen.

PDA: patent ductus arteriosus. RR: relative risk. 95% CI: 95% Confidence Interval.

(1st, 2nd) first and second course of treatment. N: number. (%): percent. IV: intravenous.

Table 2: Distribution of all pts in group and subgroup, and response to 1st and 2nd course of treatment.

Variable	Group I (n: 104)	Group 2 (n: 104)	p value	RR	95% CI
Oliguria, n (%)					
Total pts	20/104 (19.2)	10/104 (9.6)	0.038	0.564	(0.381–0.816)
<1000 g	11/32 (34.3)	7/36 (19.4)	0.045	0.662	(0.67–0.92)
<1250 g n(%)	7/37 (19)	2/26 (7.7)	0.123	0.623	(0.17–0.99)
<1500 g n(%)	2/35 (5/7)	1/42 (2.4)	0.114	0.334	(0.43–.987)
Elevated serum creatinine, n (%)					
Total pts	15/104 (14.4)	8/104 (7.7)	0.034	0.458	(0.561–0.823)
<1000 g	7/32 (21.9)	6/36 (16.7)	0.123	0.78	(0.43–1.56)
<1250 g n(%)	6/37 (16.2)	2/26 (7.7)	0.041		
<1500 g n(%)	2/35 (5.7)	0/42 (0)	0.323		
Necrotizing enterocolitis, n (%)					
Total pts	6/104 (5.8)	4/104 (3.9)	0.233	0.334	(0.218–0.995)
<1000 g	2/32 (6.2)	2/36 (5.6)	<0.324		
<1250 g n(%)	3/37 (8.1)	2/26 (7.7)	<0.331		
<1500 g n(%)	1/35 (2.9)	0/42 (0)			
UGI bleeding, n (%)					
Total pts	12/104 (11.5)	5/104 (4.8)	0.048	0.82	(0.36-0.87)
<1000 g	6/32 (18.7)	4/36 (11)	0.252	0.72	(0.215–1.62)
<1250 g n(%)	5/37 (13.5)	1/26 (3.8)	0.051	0.355	(0.112–0.991)

<1500 g n(%)	1/35 (2.9)	0/42 (0)			
Group 1: control group treated with intravenous indomethacin. Group 2: treated with oral ibuprofen. P Value: probability of chance. RR: relative risk. 95%CI: 95% confidence interval. N: number. (%): percent.					

Table 3: Complications: oliguria, elevated serum creatinine, NEC and UGI bleeding.

Clinical data and information were collected from the medical records. Patient divided for two group: group 1 which was considered as control group and given IV indomethacin as conventional treatment, and group 2 was given oral ibuprofen as new modality of treatment. During the study period, total admission to our NICU are 3501 pts (Table 1). Preterm infants < 34 wk gestational age are 1702 pts. In 1100 pts birth weight was <1500g. Isolated PDA diagnosed in 440 pts (40%) infants. 302 pts (68.7%) had symptomatic PDA and medical treatment was indicated due to; respiratory distress, increased oxygen requirements, apnea, tachycardia, bounding pulse, widened pulse pressure, and evidence of renal dysfunction. Random retrospective review of 208 files (104 for each group) was done and included in this study (Tables 1 and 2). Closure of PDA was achieved in 93/104 (89.4%) of the infants in the intravenous indomethacin group 1, and in 95 (91.3 %), (p: 0.443), of the infants in the oral ibuprofen group. The subgroup analysis revealed that in both IV indomethacin and oral ibuprofen the treatment was more effective in closing PDA in patients with higher birth body weights, (94.3- 95.2%) in pts >1250 and closure rate: (89.2-92.3%) in infants weighing >1000 g; and (84.4- 86.1%) for infants weighing <1000 g. However, there was no significant difference in the rate of closure between the three subgroups (Table 2). By the comparing of group 1 and group 2: failure to close the PDA with intravenous indomethacin occurred in 11 (10.6%) versus 9 (8.7%) infants respectively. Among them, oliguria occurred in 20 (19.2%) versus 10 (9.6%) infants, elevation of serum creatinine seen in 15 (14.4%) versus 8 (7.7%), UGI bleeding occurred in 12 (11.5%) versus 5 (4.9%), and NEC in 6 (5.8%) versus 4 (3.9%) respectively. Surgical PDA ligation was needed in 5.7% of pts in group 1 versus 4.8% of pts in group 2 (Table 2). Elevation of serum creatinine developed in 15 (14.4%) in group 1 versus 8 (7.7%) in group 2. It was significantly lower in Group 2 than in group 1. (p: 0.034, relative risk, RR: 0.458, 95% CI: 0.561–0.823), (Table 3). The subgroup analysis revealed that serum creatinine levels were significantly lower among pts in group 2 with birth weight <1250 g (p<0.123). Oliguria developed in 20(19.2%) infants in group 1versus10 (9.6%) in group 2 (p: 0.035, RR: 0.553, 95% CI: 0.381–0.816). The incidence rates of upper gastrointestinal hemorrhage was significantly lower in group 2, 5(4.9%) versus 12 (11.5) group I. [P: 0.048, RR 0.85, 95% CI (0.37-0.88)], while there was no significant decrease in the incidence of NEC between both groups and subgroups, (5.8% versus 3.9%). P: 0.233 (Table 3).

Discussion

Many Clinical trials have shown that ibuprofen is as effective as indomethacin for the treatment of PDA in preterm infants [3,4]. Oral ibuprofen were proved to be as efficient as intravenous indomethacin with less adverse effects, then its simple administration and lower cost would be important advantages [5,6]. Our study was designed with sufficient power for determining whether oral ibuprofen and intravenous indomethacin treatments are equally efficacious in PDA closure. The incidence of PDA in preterm neonates and VLBW infants in our study was approximately 40%, a rate that is similar to that reported in Saudi Arabia and in international studies [1,2]. As a result of our study, the closure rate of PDA with intravenous indomethacin was (89.4%) versus (91.3%) with oral ibuprofen which was similar to other published study [1,13] and also indicated that PDA closure in VLBW infants is at least as effective as closure with intravenous indomethacin. Recent meta-analyses of studies revealed that oral ibuprofen and intravenous indomethacin are equally effective [7-9]. The review of several studies reported that ibuprofen was as effective as indomethacin in closing PDA and that ibuprofen reduces the risk of developing complications [11]. Oral ibuprofen for closure of PDA in premature infants was first used in 2000. Since then, a number of trials have been conducted to evaluate the efficacy of oral ibuprofen for closure of PDA. There is no significant difference in the rate of closure of PDA in preterm infants between oral and intravenous ibuprofen [12,13,16], also there was no significant difference in failure rate of PDA closure between two type of treatment [4,10,11]. In clinical practice, if the medical treatment is contraindicated or patient is unstable, surgical PDA ligation is needed. According to our study, the two groups who received medical treatment rarely required further surgical PDA ligation. Our study was done to compare the effectiveness of orally administered ibuprofen with that of intravenously administered indomethacin at closing PDA among preterm infants very low birth body weight. We found that the rate of closure of PDA tended to be higher among infants with a higher birth body weight in both treatment groups. There was no significant difference in closure rate between patients that received oral ibuprofen and those that received intravenous indomethacin in each subgroup but the complications were significantly less with oral ibuprofen (Table 3). This tendency of higher rate of PDA closure among preterm infants who received medical treatment with higher birth body weights may be meaningful in clinical practice. Oral ibuprofen therapy was associated with acute renal failure in extremely low birth weight (VLBW) infants [11,13] In our study the complications developed in the preterm infants with birth weight <1500 g, in group 1 and group 2 as oliguria in 20pts versus 10, elevated serum Creatinine in 15 pts versus 8 pts, upper gastrointestinal bleeding 12 pts versus 5 pts, and NEC in 6 pts versus 4 pts respectively, (Table 3). The lower body weight premature infants had more complications. In our analysis, the incidence of all associated complications was lower in the oral ibuprofen group than in the intravenous indomethacin group. It appears that oral ibuprofen resulted in fewer renal and gastrointestinal adverse events than intravenous indomethacin as in many reported international studies [11-15].

Study Limitation

In spite of the study power and good sample size, there are limitations in applying the results of our study because of its retrospective design. Although the infants in our study were not randomized, the characteristics of the infants in the two groups were similar and there were no major changes in clinical practice during the

7 year study period. Despite these limitations, the final result still contributes valuable information on the feasibility of using oral ibuprofen in treatment of PDA closure in premature infants. Larger, prospective randomized studies are needed to clarify the efficacy, safety and other significant complications like acute renal failure and intraventricular hemorrhage with both type of treatment. Also follow up for longer time is needed.

Conclusions

In preterm infants with birth body weights <1500 g, oral ibuprofen is as effective as intravenous indomethacin for closure of PDA and is associated with significantly less adverse effects.

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