RESEARCH PAPER

Patent Ductus Arteriosus in Infants <29 Weeks Gestation – Outcomes and Factors Affecting Closure

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Objective: To determine Patent ductus arteriosus (PDA) closure rates for extremely preterm infants in a tertiary care centre, factors affecting response to indomethacin and outcomes of these infants relative to their PDA status.

Setting: Neonatal intensive care unit in tertiary-care children's hospital.

Design: Retrospective medical record review.

Methods: A retrospective chart review of all infants <29 weeks gestation between 1st Jan 2003 and 30th June 2006 was carried out. Multiple courses of standard intravenous indomethacin (dose: 0.2 mg/kg 12 hourly; 3 doses) followed by a tail course (0.1 mg/kg/day; 3 doses) were used to treat PDA depending on clinical and hemodynamic status. Data on demographic characteristics, PDA status, use of indomethacin, and outcome factors such as chronic lung disease and mortality were collected.

Results: A total of 166 infants were identified in the study period, of which 15 were excluded. The median gestation was 27 weeks [IQR (25, 28)] and the mean (SD) birthweight was 950 (244) grams. The remaining infants (*n*=151) were divided into three groups. Group1 (*n*=47): no or non-significant PDA, Group 2 (*n*=91): significant PDA closed after indomethacin treatment (≥ 1 course) and Group 3 (*n*=13): significant PDA not responding to indomethacin. The closure rate of PDA with indomethacin treatment (group 2) was 87%. A low gestational age < 26 weeks (OR 5.6, 95% CI 1.6-19.9) and female sex (OR 5.8, 95% CI 1.5-22.8) was associated with poor response to indomethacin in our study population.

Conclusions: Multiple indomethacin courses using the standard dosing approach result in high PDA closure rates for infants < 29 weeks gestation.

Key words: *Ductus arteriosus, Indomethacin, Infant, Preterm.*

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In preterm infants more than 30 weeks of gestational age, the ductus arteriosus usually closes by 5 days. In contrast, in two-thirds of the infants less than 30 weeks of gestational age, who often have significant lung disease, it does not close by 5 days of age [1,2].

A large left-to-right shunt has the potential to contribute to severe complications such as congestive cardiac failure, chronic lung disease, necrotizing enterocolitis and intraventricular hemorrhage (IVH) in low birth weight infants [3,4]. However, meta-analyses of randomized controlled trials of the use of indomethacin for prevention and treatment of PDA have not documented a decrease in the incidence of these morbidities, despite success in closure of the PDA [5,6].

Although indomethacin has been widely accepted to be effective in closing PDA in LBW infants, it may not be effective in up to 40% of cases [2, 9]. Reopening of the ductus after initial closure also occurs in 20% to 100% of treated infants [9, 10]. Indomethacin is also known to be associated with adverse effects such as renal dysfunction, electrolyte abnormalities, thrombocytopenia, intestinal perforation and gastrointestinal bleeding [11]. Furthermore, there is no consensus on the timing, dosage and the duration of indomethacin treatment for PDA. Risk factors for subsequent reopening of the PDA also remain poorly defined. We studied the PDA closure rates for extremely preterm infants at our center and the factors determining a poor clinical response to indomethacin treatment. The incidence of the adverse effects in the study population was also investigated.

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METHODS

All infants of gestational age 28 weeks or less, born between 1st January, 2003 and 30th June, 2006 at a Level 3 Neonatal Intensive Care unit (NICU) in New South Wales were included in this retrospective, case-control study. Infants who were out-born and admitted were also included. Infants who died within the first 72 hours of life and those with congenital heart disease were excluded, as

it was considered too short a time for closure of PDA to be achieved with any treatment, medical or surgical. The study design was approved by the Human Research Ethics Committee of the Local Area Health Service.

After collecting baseline and clinical data, infants were classified into three groups for further analysis. Group I included infants with closed PDA or non-significant PDA, Group II included infants who had a significant PDA which closed with medical treatment, and Group III included infants where the PDA failed to close after multiple courses of indomethacin.

Clinical examination and echocardiogram findings were used to evaluate the PDA before commencing treatment. All echocardiograms were performed and reported by a consultant pediatric cardiologist. A significant PDA was defined as one that had one or more of the following clinical signs - (*i*) unexplained worsening of respiratory support, (*ii*) widening of the blood pressure amplitude or low blood pressure, or (*iii*) systolic or continuous murmur; *and* met one or more of the following echocardiographic criteria: (*i*) LA/Ao ratio of >1.4, (*ii*) ductal diameter more than 1.5 mm, and (*iii*) moderate to large left to right shunt. If PDA was considered significant enough to cause clinical signs in the absence of all the echocardiographic criteria, the decision to treat was at the discretion of the on-call neonatologist.

Response to indomethacin was defined as closed or non-significant PDA confirmed on echocardiogram after treatment with indomethacin. Dosage regimens used for a course of indomethacin were 0.2mg/kg × 3 doses, 12 hrs apart or 0.1mg/kg × 5 to 6 doses, 24 hr apart. If anything other then above was used it was specifically elaborated. A tail course (0.1mg/kg every 24 hr × 3 doses) was used immediately following the initial indomethacin course, if considered to be indicated by the on-call neonatologist, and counted as part of one indomethacin course. Prophylactic indomethacin was not used during the study. The decision regarding the dosage to be used and number of courses to be given were at the discretion of the on-call neonatologist. Indomethacin was administered via the intravenous route for all the study patients.

Some of the outcomes assessed included closure of PDA, mortality, surgical ligation, chronic lung disease (CLD) (oxygen requirement or pressure support at 36 weeks corrected gestation age), intraventricular hemorrhage (grade 3-4), proven necrotizing enterocolitis (NEC), duration of hospital stay, duration of assisted ventilation, pulmonary hemorrhage and, retinopathy in the study population. The definitions used for each of the outcome were as mentioned in the Report of the Neonatal Intensive Care Units (NICUS) data collection [14].

Statistical analysis: Data were analyzed using Intercooled STATA version 10.0 for Windows. Categorical data were summarized using frequency distributions with 95% confidence intervals and continuous data were described using mean (standard deviation) when normally distributed or using medians and interquartile ranges otherwise. Categorical variables were analyzed using the Fisher exact test while ANOVA and Kruskal-Wallis tests were used for continuous variables as appropriate. Regression analysis was used to adjust for variations in study groups with respect to gestational age and CRIB score.

RESULTS

A total of 166 infants born at <29 weeks gestation were admitted to the neonatal intensive care unit during the study period. Fifteen infants were excluded from the analysis (4 had congenital heart disease, 10 died within 72 hrs, and 1 infant was extremely premature with extensive IVH, where a decision on withdrawal of support was made within 72 hours without any treatment offered for PDA). The data on the remaining 151 infants were analysed. 104 infants (69%) were diagnosed as having a significant PDA and were treated with indomethacin. 9 of these infants had significant clinical symptoms to warrant treatment inspite of not fulfilling the echocardiographic criteria (7 in group II and 2 in group III). 91 (87.5%) of those infants responded to multiple courses of indomethacin and were classified as Group II. Of the 13 infants (Group III) who did not respond to indomethacin, 7 underwent surgical ligation and 6 were observed expectantly with closure of PDA on follow up. The infants with PDA that did not respond to indomethacin (group III) were born at lower gestation (P=0.0014) and were more likely to be female (P= 0.019) (***Table* I**). Infants with gestation less than 26 weeks were 5.6 times (95% CI 1.6-19.9) and female infants were 5.8 (95% CI 1.5-22.8) times more likely to not respond to indomethacin as compared to those who responded to indomethacin. There were 9 infants in group III and 25 infants in group II, which were less than 26 week gestation. Chorioamnionitis, ethnicity, intrauterine growth retardation, need for resuscitation, maximum oxygen required, fluid management, and need for inotropes were analyzed and not significantly different between the groups.

An echocardiogram was performed in all infants (n = 141), except 10 who were clinically well and asymptomatic for PDA. Of the 104 infants treated with indomethacin, only 12 infants received three or more courses of indomethacin while 70 infants responded to one course of indomethacin. If the duct did not close by the third course, then it was unlikely to close with further

TABLE I DEMOGRAPHICS OF THE STUDY POPULATION

	All (n=151)	*Group 1(n=47)*	*Group 2(n=91)*	*Group 3 (n=13)*	*P value*
Gestation*	27 (25, 28)	27 (26, 28)	27 (25, 28)	25 (24, 27)	0.001
Birthweight$	950 (244)	941 ± 223	967 (257)	860 (218)	0.42
Male gender#	91 (60.3)	30 (63.8)	58 (63.7)	3 (23)	0.019
Antenatal steroids (complete course) #	90 (59.6)	30 (63.8)	53 (58.2)	7 (53.8)	0.71
CRIB score*	4 (2, 7)	4 (2, 6)	4 (2, 7)	8 (2, 9)	0.16
Surfactant#	101 (66.9)	24 (51)	68 (74.7)	9 (69.2)	0.088
Sepsis (culture proven) #	66 (44.3)	17 (36.2)	41 (46)	8 (61.5)	0.24

**Median (IQR1, IQR3); # Number (%); (SD); $Mean (SD).*

courses of indomethacin. The median age beyond which duct failed to close was 29 days (IQR1 = 12, IQR3 = 39). No significant differences between group 2 and group 3 were observed with regards to the age at the time of first indomethacin dose, PDA size, LA/Ao ratio, and PDA shunt (***Table* II**). Indomethacin was well tolerated in the study population with 26.9% infants experiencing adverse effects; all of these were transient and non life threatening. The specific adverse effects were thrombocytopenia (infants), and low urine output <0.5 mL/kg/hr, high creatinine >150 mmol/L in 1 infant. Hyponatremia (Na <130 mmol/L) occurred in 18 infants in group II and 6 in group III.

***Table* III** shows the outcome of all the study infants. The duration of CPAP, duration of ventilation, and length of stay remained significantly different even after correcting for gestation age and CRIB score, with infants in group III remaining on CPAP for a longer duration (43.5 days), requiring prolonged ventilation (4.3 days), and requiring hospitalisation for a longer time (102.8 days).

DISCUSSION

A significant PDA was diagnosed in 69% of the infants born at less then 29 week gestation, which is similar to the incidence reported in literature [2,3]. We found a high response rate (87.5%) with multiple courses of standard dosage of indomethacin, with or without a tail course. There are very few studies which have reported the closure rate after multiple courses of indomethacin. The response rate of 60 to 80% to standard dosage of indomethacin reported by other authors [2,9] is less than the response rate seen in our study population. Prolonged course of indomethacin compared to the short course has not been reported to be more effective either [16]. Several population-based, observational studies have used higher doses of indomethacin to treat infants where PDA failed to close with conventional dosing. These studies report PDA closure rates of more than 90% with a stepwise, escalating approach to indomethacin dosing [17-19]. A recent multi-center randomized controlled trial reported contrasting findings with little effect on the rate of PDA closure with indomethacin concentrations above the levels achieved with a conventional dosing regimen but reported higher rates of moderate/severe ROP and renal compromise [20].

TABLE II PATENT DUCTUS ARTERIOSUS STATUS AND INDOMETHACIN USE

	Group II (n=91)	*Group III (n=13)*
LA/Ao Ratio*	1.4 (1.2,1.6)	1.45 (1.2, 1.6)
PDA Size*	2 (1.5,2.3)	2 (1.6, 2)
Moderate to Large#	59 (82)	10 (91)
Postnatal age* (d)	3 (2,4)	4 (3,4)
>1 course, No (%)#	21 (23)	12 (92.3)
>2 courses, No (%)##	6 (6.6)	6 (46)
Adverse effects, No (%)$	21 (23%)	7 (53.8%)

**Median (IQR1, IQR3); # P=0.0001; ##P=0.001; $P=0.039.*

The number of infants who underwent surgical ligation during the study period was 7 (7%), which in effect leaves 93% of the infants managed non-surgically. This is comparable with ANZNN statistics of 9% of the newborns between 23 and 27 weeks who underwent surgical ligation [14].

Several authors have reported low gestation to be a risk factor for poor responsiveness [21-23], while gender has not been reported by any. However, it has been shown that neonatal mortality, short-term morbidity and adverse neurodevelopmental outcomes are higher among male than female infants [24]. Poor response to indomethacin is also reported to be more common in extremely LBW infants and in infants with infection or advanced postnatal age [25-27]; however, we did not note those differences. The reasons for non-responsiveness of PDA to indomethacin in preterm infants remains ill defined.

Our findings conform to those of other studies in that

WHAT IS ALREADY KNOWN?

- There is no consensus on the dosage and the duration of indomethacin treatment for PDA, and it may not be effective in 10-40% cases.

WHAT THIS STUDY ADDS?

- Multiple indomethacin courses (up to a maximum of 3) using the standard dosing approach resulted in high closure rates for infants less then 29 weeks of gestation.
- If PDA remained open despite three courses of indomethacin or till 4 weeks of age, it was unlikely to close by medical treatment.

treatment was not found to alter the incidence of neonatal morbidities associated with PDA [28]. Based on the available evidence, it is difficult to infer if the reported association between a persistent PDA and other neonatal morbidities is a result of left to right shunt itself, the pharmacotherapies used, or the immaturity of the infant who is likely to develop a PDA. However, unlike the meta-analysis by Cooke, *et al*. [6], we did find that significant PDA was associated with need for prolonged respiratory support (CPAP and ventilatory requirement), and increased length of stay which does lead to significant utilization of resources. There were no deaths in infants in group III who did not respond to indomethacin, which needs to be interpreted with caution in the light of few infants in that group.

None of these adverse effects were related to the duration and total dosage of indomethacin (Group II and III), which is similar to that reported by other authors [29,30].

The limitation of our study is that it is a retrospective analysis. There was no long-term data available for the study population. The infants were treated after they developed symptoms so the results may not be applicable to prophylactic treatment or presymptomatic treatment based on echocardiography. The advantage of this strategy is that it allows spontaneous ductal closure thereby avoiding overtreatment with indomethacin. Some of the babies were treated with indomethacin just based on clinical symptoms, which may represent liberal use; however, the numbers of such babies were very small. Such a pragmatic approach allows for clinical acumen to guide treatment rather than just relying on echocardiographic cut-offs. The study base is well defined with controls drawn from the same population as the cases. It is also one of the few studies to report on the closure rate of PDA in the preterm population after multiple courses of standard dose of intravenous indomethacin therapy.

TABLE III OUTCOME OF STUDY INFANTS (*N*=151)

	All	*Group I*	*Group II*	*Group III*	*P value**
NEC[#]	15 (9.9%)	8 (17%)	7 (7.7%)	0	0.40
IVH (Grade 3/4) or PVL[#]	16 (10.6%)	5 (10.6%)	10 (11%)	1 (7.7%)	0.66
ROP (any)[#]	67 (50.8%)	20 (51.3%)	38 (47.5%)	9 (69.2%)	0.56
Pulmonary hemorrhage[#]	8 (5.3%)	1 (2.1%)	7 (7.7%)	0	0.77
Duration of CPAP (hrs)^	720 (240, 991)	336 (58, 934)	729 (326, 994)	1045 (890, 1387)	0.001
Duration of ventilation (hrs)^	49 (0, 177)	0 (0, 63)	83 (0, 91)	104 (34, 556)	0.027
CLD (Oxygen at 28 d)[#]	93 (66%)	19 (46.3%)	61 (70.1%)	13 (100%)	0.44
Oxygen at 36 wks[#]	49 (35.8%)	9 (22%)	30 (36.1%)	10 (77%)	0.45
Home oxygen[#]	30 (24.8%)	4 (12.1%)	20 (26.7%)	6 (46.1%)	0.47
Postnatal dexamethasone[#]	5 (4.5%)	1 (3.4%)	1 (1.4%)	3 (23%)	0.50
Length of stay (d)[@]	65.9 (34)	55.6 (35.8)	65.9 (28.8)	102.8 (38.4)	0.004
Mortality[#]	15 (9.9%)	6 (12.8%)	9 (9.9%)	0	0.42

*^Median (IQR^1, IQR^3); [#]Number (%); Mean (SD); ROP: Retinopathy of prematurity; CLD: Chronic lung disease; IVH: Intra-ventricular hemorrhage; NEC: Necrotizing enterocolitis. * P value adjusted for gestation and CRIB score.*

In summary, multiple indomethacin courses (up to a maximum of 3) using the standard dosing approach resulted in high closure rates (87.5%) for infants less then 29 weeks of gestation in our NICU. Decreasing gestation and female gender were the only indicators for predicting response to indomethacin. If PDA remained open despite three courses of indomethacin or until 4 weeks of age, it was unlikely to close by medical treatment. Indomethacin in the dosage used was well tolerated in the study population.

Contributors: JT conceived and designed the study, analyzed data and revised the manuscript. JT will act as the guarantor of the study. HP collected data, helped in data analysis and drafted the manuscript. VK helped with data collection and revised the manuscript. The final manuscript was approved by all the authors.

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