Predictors of failed closure of patent ductus arteriosus with indomethacin

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ABSTRACT

Introduction: The aim of this study was to determine predictors of failed closure of patent ductus arteriosus (PDA) following a single course of indomethacin in symptomatic preterm infants.

Methods: This prospective observational study was carried out on 60 preterm infants weighing less than 1,750 g with symptomatic PDA confirmed by echocardiography. At a median age of 7.0 days (interquartile range 4.0), they were given indomethacin of 0.1 mg/kg/day intravenously daily for six days. Closure of PDA was reassessed by echocardiography upon completion of therapy.

Results: The PDA of 40 percent (n=24) of these infants remained patent. Forward logistic regression analysis showed that the only significant predictors of failed PDA closure in these infants were: PDA size (adjusted odds-ratio [OR] is 7.0; 95 percent confidence interval [CI] of OR is 2.0, 24.8; p-value is 0.002), birth weight (adjusted OR is 0.996; 95 percent CI of OR is 0.993, 1.000; p-value is 0.03) and platelet count (adjusted OR is 0.987; 95 percent CI is 0.975, 1.000; p-value is 0.045). Gestational age, maternal age and left atrium/aorta ratios were not significant predictors.

Conclusion: Larger PDA, lower birth weight and lower platelet count were significant predictors of high failure in indomethacin therapy given late at one week of life.

Keywords: indomethacin therapy, patent ductus arteriosus, preterm infants

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INTRODUCTION

Patent ductus arterious (PDA), a common problem in preterm infants, is associated with a number of complications including prolonged requirement for ventilatory support, increased risks of infections, bronchopulmonary dysplasia and heart failure[1-3]. Indomethacin, an inhibitor of synthesis of prostaglandins, has been found to be a very useful drug for closure of PDA in preterm infants[4,5]. However, despite treatment with this drug, failure of closure has been reported to be as high as 21%[6].

Based on univariate analyses, a number of potential risk factors have been identified to be associated with failed closure of PDA using indomethacin. Review of the literature published between 1966 and 2002 via MEDLINE showed that there is only one multivariate analysis reported on significant predictors associated with failed closure of PDA following treatment with indomethacin[7]. In that study, late treatment with indomethacin, larger size of PDA, and lower gestational age were some of the significant predictors identified, after controlling for various confounders[7]. As PDA is associated with high morbidity and mortality, surgical closure should be considered early in cases when medical treatment fails. The objective of the present study was to determine the significant predictors of failed closure of PDA following a single course of indomethacin, so that infants who required surgical ligation could be identified earlier to minimise associated complications.

METHODS

This was a prospective observation study carried out in the neonatal intensive care unit (NICU) of Hospital Universiti Kebangsaan Malaysia over a 33-month period, between January 1, 2002 and September 30, 2004. The study protocol was approved by both the hospital's scientific and ethics committees. During the study period, any infants suspected to have symptomatic PDA (defined as presence of a systolic heart murmur and/or easily palpable popliteal pulses associated with tachycardia >160 beats/minute) were evaluated using echocardiography.

Echocardiography was performed by one of

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the two cardiologists using an ultrasound machine with colour Doppler moder (Apogee 800 Plus, ATL Ultrasound Inc, Bothell, WA, USA) and a 7.5-MHz transducer. The ductus arteriosus was evaluated from the left parasternal long axis and short axis view, as well as the suprasternal view. The ductal diameter size was measured (in millimetres) via the short axis view at the pulmonary area, and the left atrial (LA) and aortic (AO) root diameters were measured via the left parasternal long axis view using M-mode. Both continuous wave and pulse wave Doppler modes were used to confirm the presence and direction of ductal flow. All echocardiograms were recorded on videotapes and interpreted by one cardiologist (BAA). A haemodynamically-significant PDA based on echocardiographical findings was defined as one with an internal ductal diameter of ≥1.5mm and/or with an LA/AO ratio ≥1.5[8].

The inclusion criteria were all preterm infants with symptomatic PDA confirmed by echocardiography, of gestational age less than 37 weeks, birth weight less than 1,750 g, and commenced on indomethacin treatment by the neonatologists in charge. The exclusion criteria were presence of a ductal dependent cardiac lesion, persistent pulmonary hypertension, gross congenital abnormalities, or birth weight greater than 1,750 g.

The dose of indomethacin used for closure of PDA in this NICU during the study period was 0.1 mg/kg/day given intravenously daily for six days. Indomethacin was withheld when any of the following conditions was present: urine output less than 1 ml/kg/h for more than six hours, thrombocytopaenia of $<60 \times 10^9/\mu L$, bleeding diathesis, serum bilirubin >200 μmol/L, suspected necrotising enterocolitis, renal impairment (serum creatinine >141 μmol/L), or ductal dependent congenital heart disease.

Within 48 hours of completion of a course of indomethacin treatment, echocardiography was repeated to assess ductal size. A second course of indomethacin was given when a PDA was still present without associated contradictions to therapy. Following echocardiographical confirmation of closure of PDA, infants were monitored closely for clinical evidence of re-opening of PDA. Repeat echocardiography was carried out on any infant suspected of having re-opened PDA. Congestive heart failure was diagnosed when there was persistent tachycardia (>160 beats/minute), tachypnoea (>60 breaths/minute), cardiomegaly and enlarging hepatomegaly.

During indomethacin therapy, full blood count and renal profiles of infants were monitored before the onset and on the third or fourth day of therapy. Indomethacin therapy was stopped when an infant developed any of the contraindication described above. Based on an estimated 25% rate of failed closure of PDA by indomethacin therapy[6], with an absolute precision of 10% at 90% confidence level, a minimum sample size of 51 infants was required.

Variables of infants with and without PDA closure following indomethacin therapy were compared. The chi-square test (or Fisher exact test for variables with an expected value of less than five) was used for analysis of categorical variables. For continuous variables, the Student's t-test (unpaired) was used for analysis of variables with normal distribution and the Mann-Whitney U test for analysis of variables with skewed distribution. Logistic regression analysis was subsequently carried out to identify the significant risk factors associated with failed first course of indomethacin therapy. The status of PDA after first course of indomethacin therapy was used as the dependent variable while potential risk factors (weight, gestational age, maternal age, platelet count prior to first course of indomethacin therapy, PDA size and LA/AO ratio prior to therapy) identified during univariate analysis with p-values of <0.05 were used as independent variables. p-values of less than 0.05 were considered to be statistically significant.

RESULTS

During the study period, 380 preterm infants weighing <1,750 g were admitted to the NICU. Of these, 60 (15.8%) developed symptomatic PDA at a median age of 5.0 days (interquartile range [IQR]=3.0). None of them had other cardiac lesions. Following a first course of indomethacin at a median age of 7.0 days (IQR=4.0), the PDA of 40% (n=24) remained patent (Fig. 1). 14 (23.3%) infants received a second course of indomethacin therapy and two (3.3%) a third course. 13 (21.7%) infants subsequently had surgical ligation of PDA. 11 (18.3%) infants died despite treatment. No infants who survived, developed evidence of re-opening of PDA.

The maternal and demographical data of infants with and without closure of PDA by a first course of indomethacin were compared (Table I). Except for birth weight, gestational age and maternal age, there was no significant difference in the proportions of infants with various maternal and basic neonatal factors between these two groups. Infants with failed PDA closure weighed significantly less, were of significantly younger gestational age and were born to significantly younger mothers, than infants whose PDA were successfully closed after a first course of indomethacin therapy ($p<0.05$).

Table I. Comparison of neonatal demographical and maternal factors between infants with and without closure of PDA treated with first course of indomethacin.

Maternal and neonatal variables	PDA not closed (n=24)	PDA closed (n=36)	Unadjusted odds-ratio (95% CI)	p-value
Ethnic groups (%)				
Non-Malays	9 (37.5)	12 (33.3)		
Malays	15 (62.5)	24 (66.7)	0.8 (0.3, 2.8)	0.7
Male infants (%)	12 (50)	21 (58.3)	0.7 (0.2, 2.3)	0.5
Maternal parity (%)				
0-1	16 (66.7)	18 (50)		
≥2	8 (33.3)	18 (50)	2.0 (0.6, 6.7)	0.2
PIH (%)	3 (12.5)	7 (19.4)	0.6 (0.1, 3.0)	0.7
Placenta praevia (%)	1 (4.2)	3 (8.3)	0.5 (0.01, 6.5)	0.6
Given antenatal steroid (%)	15 (62.5)	22 (61.1)	1.1 (0.3, 3.5)	0.9
			95% CI of difference between means	
Mean maternal age (years) (SD)	26.1 (4.7)	29.8 (7.0)	-6.7, -0.6	0.02*
Mean birth weight (g) (SD)	1,027 (218)	1,175 (297)	-280, -14	0.03*
Mean gestational age (weeks) (SD)	28.0 (2.5)	29.6 (2.7)	-2.9, -0.2	0.03*
Mean Apgar score at 1 minute of life (SD)	6.3 (1.9)	6.1 (1.9)	-0.8, 1.2	0.7
Mean Apgar score at 5 minutes of life (SD)	8.1 (1.2)	8.4 (1.3)	-0.9, 0.4	0.4

PIH: pregnancy-induced hypertension; CI: confidence interval; SD: standard deviation; * denotes statistical significance.

Table II. Comparison of clinical problems occurring prior to first course of indomethacin therapy between infants with and without closure of PDA by first course of indomethacin.

Clinical variables	PDA not closed (n=24)	PDA closed (n=36)	Unadjusted odds-ratio (95% CI)	p-value
RDS (%)	23 (95.8)	30 (83.3)	4.6 (0.5, 220.6)	0.2
Received surfactant therapy (%)	23 (95.8)	30 (83.3)	4.6 (0.5, 220.6)	0.2
Congenital pneumonia (%)	1 (4.2)	2 (5.6)	0.7 (0.01, 15.0)	1.0
Ventilated (%)	23 (95.8)	30 (83.3)	4.6 (0.5, 220.6)	0.2
Median duration of ventilation (days) (IQR)	4 (5.8)	2 (4.0)	-	0.08
Congestive heart failure (%)	13 (54.2)	13 (36.1)	2.1 (0.6, 6.9)	0.2
Sepsis (%)	4 (16.7)	5 (13.9)	1.2 (0.2, 6.5)	1.0
Median volume of maintenance fluid at time of diagnosis of PDA (ml/kg/day) (IQR)	150 (20)	150 (10)	-	0.6
			95% CI of difference between means	
Mean urine output before indomethacin therapy (ml/kg/h) (SD)	5.4 (1.2)	5.4 (1.4)	-0.7, 0.7	1.0
Mean Hb (g/dL) (SD)	13.0 (2.4)	13.1 (1.8)	-1.2, 1.2	1.0
Mean platelet count (10^9/dL) (SD)	137.1 (69.0)	183.4 (38.8)	-77.9, -14.8	0.005*

RDS: respiratory distress syndrome; CI: confidence interval; Hb: haemoglobin; SD: standard deviation; IQR: interquartile range; * denotes statistical significance.

Table III. Comparison of clinical variables regarding PDA and first course of indomethacin therapy between infants with and without PDA closed by first course of indomethacin.

	PDA not closed (n=24)	PDA closed (n=36)	95% CI of difference between means	p-value
Mean age of detection of PDA (days) (SD)	5.8 (3.0)	5.1 (3.4)	-1.0, 2.3	0.4
Mean PDA size prior to indomethacin therapy (mm) (SD)	2.2 (0.6)	1.4 (0.7)	0.4, 1.1	<0.001*
Mean LA/AO ratio prior to indomethacin therapy (SD)	2.0 (0.7)	1.5 (0.5)	0.1, 0.8	0.005*
Median age when indomethacin therapy was started (days) (IQR)	7.0 (3.0)	7.5 (5.0)	-	0.7
Median number of doses of indomethacin given during first course of therapy (IQR)	6.0 (3.8)	6.0 (0)	-	0.1
			Unadjusted odds-ratio (95% CI)	
Received frusemide during indomethacin therapy (%)	13 (54.2)	13 (36.1)	2.1 (0.6, 6.9)	0.2

SD: standard deviation; IQR: interquartile range; LA/AO: left atrium/aorta; CI: confidence interval; * denotes statistical significance.

Prior to a first course of indomethacin therapy, there was no significant difference between the two groups in the proportions of infants with respiratory distress syndrome (RDS), given surfactant therapy at birth, congenital pneumonia, developing congestive heart failure or sepsis, and on ventilatory support (Table II). Neither was there any significant difference in the volume of maintenance fluid given, mean urine output or mean haemoglobin level between these two groups of infants before commencement of first course of indomethacin therapy. Infants who failed to respond to a first course of indomethacin therapy had longer duration of ventilatory support than those who responded to therapy. However, this difference was not statistically significant (p=0.08). The mean platelet count of infants at the time when indomethacin was started, however, was significantly lower among infants with failed therapy (p=0.005).

There was no significant difference in the median age when symptomatic PDA was diagnosed between these two groups of infants (Table III). Neither was there any significant difference between the median ages when indomethacin was started, nor any difference in the proportion of infants given frusemide therapy (during indomethacin therapy) between the two groups of infants. However, when compared with infants whose PDA closed with therapy, infants who failed to respond to a first course of indomethacin therapy had significantly larger PDA and higher mean LA/AO ratios prior to therapy (p<0.01).

Forward logistic regression analysis showed that, after controlling for various potential confounders, the only significant predictors of failed PDA closure with a first course of indomethacin therapy were larger PDA size (adjusted odds ratio [OR]=7.0; 95% confidence interval [CI] of OR=2.0, 24.8; p=0.002), lower birth weight (adjusted OR=0.996; 95% CI of OR=0.993, 1.000; p=0.03) and lower platelet count (adjusted OR = 0.987; 95% CI=0.975, 1.000; p=0.045). Gestational age, maternal age and LA/AO ratios were not significant predictors.

Using values of estimated beta obtained from the forward regression equation mentioned above, the probabilities of failed PDA closure in symptomatic infants following a first six-day course of low dose indomethacin therapy at different birth weight, PDA diameters and platelet count could be estimated from the equation of $1/(1=e^{-Z})$, where z=5.878 + 1.952 (size of PDA) – 0.004 (birth weight) – 0.013 (platelet count); the diameter of PDA was expressed in millimetres, birth weight in grammes, and platelet count was expressed as $\times 10^3$/dL, respectively. The calculated probabilities of failed closure of PDA in symptomatic infants with normal platelet count of 150 × 10^3/dL but with different birth weight and different PDA diameter, are shown in Fig. 2.

DISCUSSION

The incidence of PDA detected in preterm infants weighing <1,750 g in this study was lower than that reported by other investigators (Van Overmeire

et al: 33%[7], Kluckow et al: 36%[8], Gersony et al: 21%[9]). One possible explanation for this was that the study was confined only to infants with clinical signs suggestive of PDA. As a result, infants with smaller PDA or who remained asymptomatic were not included in the present study. The failure rate of closing PDA with indomethacin in the present study was also higher than those reported elsewhere which had success rate as high as 79%[7,9-11]. The most likely explanations for this were the relatively later age (mean age of five days) of diagnosing PDA and the relatively later age (median age of 7.0 days) (Table III) of commencing indomethacin therapy in the present study. In a large randomised controlled study reported by Van Overmeire et al, successful closure of PDA was significantly higher among infants given indomethacin therapy at a mean age of 3.1 days (73% closure rate) than infants treated at a mean age of 7.3 days[7].

In the present study, we also found that once the PDAs of symptomatic infants failed to respond to a course of indomethacin, it was unlikely for them to respond to repeated courses of indomethacin, especially when given late (Fig. 1). Furthermore, the mortality rate (8/24 or 33.3%) of infants who failed to respond to a first course of indomethacin was much higher than that (3/36 or 8.3%) of infants with PDA which did respond. In view of the high failure rates, our data suggest that screening and indomethacin treatment for PDA should be carried out earlier, i.e. within the first three days of life. Surgical ligation should be considered early once symptomatic infants failed to respond to an early course of therapy. The favourable outcome (survival of 92.3%) of infants who underwent surgical ligation in the present study was consistent with that of Goldstein et al[12], who reported no increase in morbidity and mortality in their surgically-ligated symptomatic PDA infants when compared with those whose PDA closed spontaneously.

Our data also confirmed the findings of other investigators[7] that the size of PDA is a very important predictor of failed closure of PDA by indomethacin therapy. For example, we found that in symptomatic infants weighing 1,000 g, and with PDA diameter ≥1.5 mm and a normal platelet count, the probability of failure to respond to a single course of indomethacin given at one week of age was more than 97%. Contrary to the observation of other investigators, we did not find LA/AO ratio to be a significant predictor of failed PDA closure based on multivariate analysis. The most likely explanation was the small sample size of this study which was under-powered to detect the difference in the LA/AO ratios

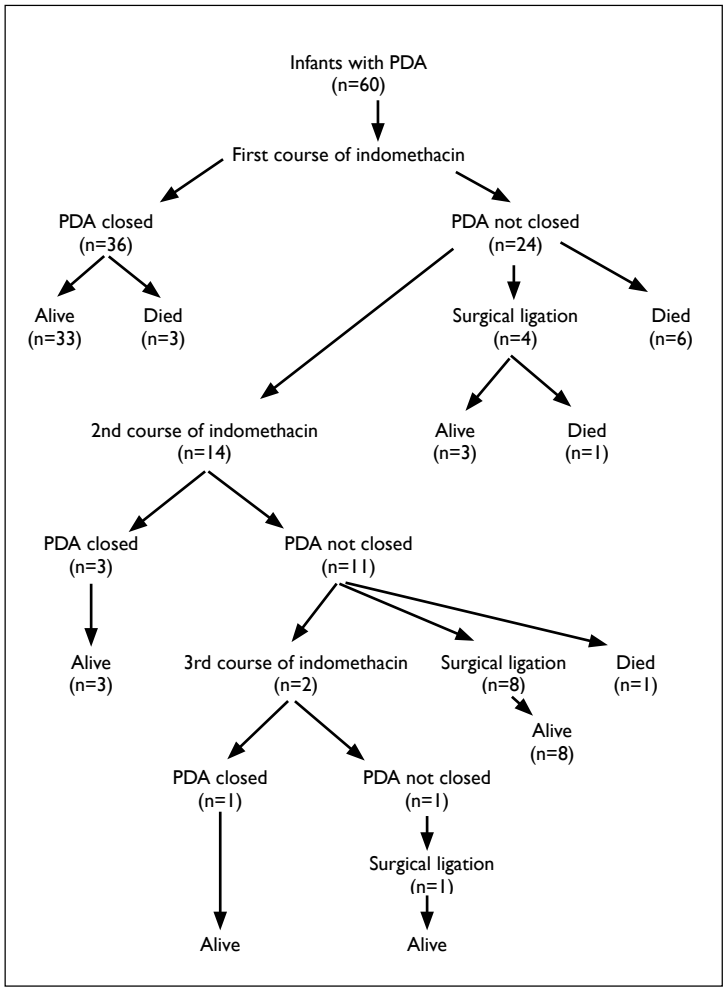

Fig 1. Outcome of infants with PDA treated with indomethacin and surgical ligation.

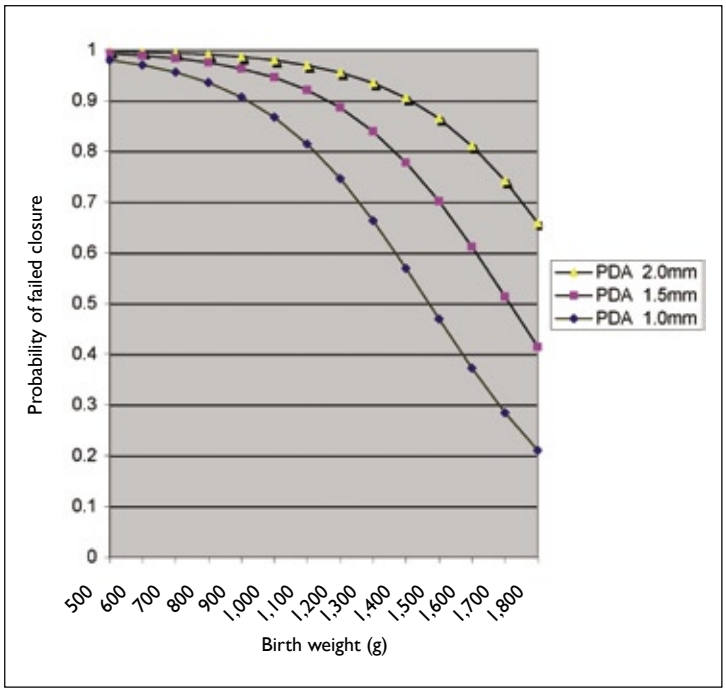

Fig 2. Probabilities of failed closure of PDA in symptomatic preterm infants with normal platelet count of 150,000/dL treated with a first six-day course of low-dose indomethacin therapy.

between the two groups of infants. Although not previously reported, our study identified two other predictors of failed closure: lower birth weight and lower platelet count. That lower birth weight was a significant predictor of failed indomethacin therapy could be explained by the relatively larger size of PDA in smaller infants, and therefore greater difficulty to close these shunts medically. As indomethacin brings about PDA closure by initiating functional closure, when a PDA is too large, complete functional closure of the ductal lumen via extensive muscular constriction cannot be achieved with this mode of therapy. Unlike the findings of other investigators, gestational age was not a significant risk factor, after controlling for various confounders. This lack of significance could partly be due to inadequate sample size recruited to determine the effect of gestational age on PDA closure.

It is not certain what exact role the lower platelet count plays in the prevention of successful closure of PDA brought about by indomethacin therapy. Our data showed that interruption of indomethacin therapy due to a falling platelet count did not account for this (Table III). One possible reason could be the prevention of thrombosis of ductal lumen during anatomical closure. Higher platelet count promotes thrombosis and therefore better luminal occlusion during the process of anatomical closure of PDA. However, this speculation is not supported by postmortem findings reported previously where thrombosis within ductal lumen was rarely observed[13].

The high mortality and morbidity rates associated with failed PDA closure in the present study were congruent with those reported in other studies. There is, therefore, a need to consider prophylactic indomethacin therapy and early surgical ligation in infants with more than 90% probability of failed therapy identified in the present study. Meta-analysis of randomised controlled trials showed that prophylactic indomethacin significantly reduces the incidence of symptomatic PDA and severe intraventricular haemorrhage[14]. However, its use is associated with an increased incidence of necrotising enterocolitis, transiently-impaired renal function and reduction of cerebral blood flow. Furthermore, its long-term neurodevelopmental outcome is still unclear[15]. In view of these findings, randomised controlled studies should be carried out to determine the risks and benefits of giving prophylactic indomethacin to preterm infants with large PDA, which have been identified to be associated with more than 90% probability of failed closure. Meanwhile, based on the results of the present study, we recommend that surgical ligation should be carried out as soon as possible in symptomatic infants weighing ≤1,100 g and with PDA diameter of ≥1.5 mm diameter after failing indomethacin therapy, in order to reduce the associated morbidity and mortality.

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