HK J Paediatr (new series) 2003;**8**:93-100

Management of Patent Ductus Arteriosus in Very Preterm Infants in the Post-surfactant Era

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Abstract Current methods of diagnosis and treatment of patent ductus arteriosus in an era in which surfactant replacement therapy is being used routinely in respiratory distress syndrome are reviewed. Surfactant results in the early development of a left-to-right ductal shunt that affects the clinical presentation of the ductus in very preterm infants. The timing and indications for echocardiography in a cohort of very preterm infants at Monash Medical Centre were reported, and a comparison was made between those whose ductus was suspected and treated early within one week with those who presented later. Necrotising enterocolitis following indomethacin was seen only with early therapy, and treatment failure required surgical closure only with late therapy. The incidence of chronic lung disease was similar in the two groups. In the post-surfactant era, the optimal protocol for the management of the ductus requires further study in very preterm infants.

Key words Echocardiography; Indomethacin; Patent ductus arteriosus; Prematurity

Introduction

In the first clinical report of successful surfactant replacement therapy in infants with respiratory distress syndrome (RDS) over two decades ago, there was a suggestion that surfactant was associated with an earlier development of patent ductus arteriosus (PDA).[1] Surfactant has been shown to reduce pulmonary vascular resistance one hour after administration, which results in a decrease in pulmonary artery pressure and an increase in left-to-right shunting through the PDA.[2,3] This may lead to haemorrhagic pulmonary oedema and the increased risk of 'pulmonary haemorrhage' in preterm infants following surfactant therapy.[4] Prophylactic use of prostaglandin inhibitors has been recommended to close the PDA after surfactant therapy.[5]

Clinical features of PDA in preterm infants classically develop late towards the end of the first week after birth and into the second week as the infant recovers from RDS.[6] Untreated, left-to-right shunting through the PDA reduces pulmonary compliance, contributing to their ventilator dependence[7,8] and increasing their risk of developing chronic lung disease (CLD).[9,10] The earlier improvement of RDS with surfactant therapy has an effect on the timing and presentation of PDA, and possibly on the response to indomethacin therapy and co-morbidities such as necrotising enterocolitis (NEC) and CLD. This review describes the current approach to the early diagnosis of PDA. Our experience in the management of PDA in a cohort of extremely preterm infants born at Monash Medical Centre over a three-year period is reported. Current options for effective and safe pharmacological closure of PDA are discussed.

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Received January 24, 2003

Diagnosis

A high parasternal systolic or continuous heart murmur is a common presenting sign. However, a murmur is audible in only 20-50% of infants with a documented PDA.[11,12] The most sensitive clinical sign is a hyperactive precordium.[13] Although a 'bounding pulse' may suggest a wide pulse pressure, the latter has not been substantiated by objective arterial blood pressure data.[14,15] PDA is associated with a reduction in both the systolic and diastolic pressure, but there is no increase in pulse pressure. Tachycardia, tachypnoea, hepatomegaly and rales on auscultation are late and inconsistent signs. A deterioration of cardiorespiratory function is often heralded in by increasing frequency or severity in episodes of apnoea and bradycardia. Infants already on assisted ventilation often experience lack of progress in weaning or worsening oxygen and ventilatory requirements. However, clinical features are generally unreliable for the early diagnosis of PDA. Echocardiagraphic evidence of a PDA is known to precede the development of signs and symptoms by a mean of two days.[16]

The electrocardiogram is usually normal. The chest X-ray may show cardiomegaly, a 'hilar flare', hazy lung fields or a complete white-out. However, radiological abnormalities are difficult to interpret in the presence of parenchymal lung disease. In one study, pulmonary plethora and cardiomegaly were present in only 30% of infants with a symptomatic PDA prior to surgical ligation.[17] Another study reported that cardiomegaly was absent in 22% of infants with symptomatic PDA.[18]

Even though clinical signs and symptoms provide important clues to the presence of a PDA, they cannot be relied upon to detect a large left-to-right ductal shunt in the preterm infant. Echocardiography is an essential tool in the diagnosis of PDA.[19] M-mode echocardiography correctly identifies about half of the infants with PDA.[20] The sensitivity of individual M-mode measurements in the diagnosis of PDA vary from 52% to 71%.[11] The ratio of the diameter of the left atrium to that of the aortic root (LA:Ao ratio) is the most sensitive of the M-mode measurements.[21] Left-to-right ductal shunting increases the volume load on the left side of the heart and dilates the left atrium. The LA:Ao ratio increases in infants with a large PDA and falls promptly after pharmacological closure.[22] A LA:Ao ratio of >1.5:1 (>1.3:1 in fluid restricted infants), a ductal diameter >1.4 mm, and retrograde diastolic flow in the descending aorta exceeding 30% of the antegrade flow, are all indicative of a large left-to-right ductal shunt.[23]

Current clinical practice in extremely preterm infants managed in individual neonatal intensive care units (NICUs) varies from (1) prophylactic treatment with indomethacin in the first 24 hours in all extremely preterm infants, to (2) routine echocardiography in the first week and pre-symptomatic treatment on ultrasound evidence of PDA, to (3) echocardiography performed only on a clinical suspicion of PDA and treatment given if the PDA is considered 'haemodynamically significant' (hsPDA), a multifactorial decision based on a combination of clinical features and ultrasound data. In the NICU at Monash Medical Centre, we follow the third of the above protocols.

The Monash Experience

We reviewed a cohort of infants consecutively born at Monash Medical Centre in the three years, from January 2000 to December 2002, with a gestational age of less than 30 weeks or a birthweight of less than 1500 grams. Those without major congenital malformation and survived 28 days were included in the study. The indications for echo-cardiography were examined, as was the age at which the PDA was first suspected. A comparison was made between those who were investigated with an echocardiogram within one week after birth for a suspected PDA and those who presented late after one week. Infants considered to have an hsPDA were treated with intravenous indomethacin 0.1 mg/kg per dose given six times on a daily basis. Surgical closure of PDA was performed when the ductus failed to close after two courses of indomethacin or when indomethacin was contraindicated. Statistical analyses were performed using ANOVA, Kruskal-Wallis analysis of variance on ranks, chi square test, and Fisher exact test (Sigmastat).

Of the 272 extremely preterm infants, 124 infants (46%) had echocardiographic assessment for a suspected PDA, of whom 57 (47%) infants had their first study within one week after birth and 67 (53%) infants after one week. The suggestive clinical features that led to echocardiographic assessment were an audible heart murmur (54%), failure to wean from ventilation (35%), persistent hypotension (10%), blood in the endotracheal aspirate suggestive of pulmonary oedema or pulmonary haemorrhage (3%), and increased heart size on the chest X-ray (4%) (Table 1). Sixty-one (22%) of the 272 extremely preterm infants were treated with indomethacin. Only 15 (26%) of the 57 infants who had an early echocardiogram within one week had indomethacin therapy, in contrast to 46 (69%) of the 67 infants who had a late echocardiogram. Of the remaining

63 infants who did not receive indomethacin, 34 had only a small PDA and were not treated, and 29 did not have a PDA.

Comparison of Infants With and Without a hsPDA

Among the 95 infants who were diagnosed to have a PDA on echocardiogram, the 61 infants who had a hsPDA and were treated with indomethacin compared to the 34 infants who had a small PDA and were not treated with indomethacin, had a significantly lower birthweight and lower gestational age (Table 2). The LA:Ao ratio was >1.5 in 51 (84%) of the 61 infants who were treated with indomethacin. Infants who had a hsPDA, compared to those with a small PDA, had a significantly longer duration of oxygen therapy and assisted ventilation, and significantly more remained on assisted ventilation at 36 weeks post-conceptual age.

Comparison of Infants with Early and Late Treatment

Among the 61 infants who had indomethacin therapy, there was no significant difference in birthweight or gestational age between the 15 infants who had an echocardiogram early and were treated with indomethacin within one week after birth compared to the 46 infants who were investigated late and were treated after one week (Table 3). There was no significant difference in their LA:Ao ratios, duration of oxygen therapy and assisted ventilation, and the number who remained in oxygen or on assisted ventilation at 36 weeks post-conceptual age. Indomethacin therapy was

Table 1 Indications and timing of echocardiographic assessment

	Early ≤7 days (n= 57)	Late >7 days (n= 67)
Heart murmur	29 (51%)	40 (60%)
Failure to wean from ventilation	10 (18%)	34 (50%)
Persistent hypotension	12 (21%)	1 (1%)
Pulmonary oedema/haemorrhage	3 (5%)	1 (1%)
Cardiomegaly on chest X-ray	1 (2%)	4 (6%)
Miscellaneous	0 (0%)	5 (7%)

Table 2 Comparison of infants with and without hsPDA

	hsPDA (n=61)	No hsPDA (n=34)	p value
Birthweight (g, mean±SD)	848±250	1027±289	0.002
Gestation (wk, median & quartiles)	26 (25, 27)	28 (26, 29)	0.003
LA:Ao ratio (mean±SD)	1.70±0.04	1.49±0.34	0.001
Oxygen therapy (d, median & quartiles)	68 (42, 124)	43 (17, 71)	0.011
Assisted ventilation (d, median & quartiles)	63 (36, 80)	40 (16, 60)	0.002
Oxygen therapy at 36 wk post-conceptual age	32 (52%)	12 (34%)	0.187
Assisted ventilation at 36 wk post-conceptual age	26 (43%)	6 (18%)	0.031

Table 3 Comparison of infants with early and late treatment

	Early treatment (n=15)	Late treatment (n=46)	p value
Birthweight (g, mean±SD)	884±203	832±262	0.48
Gestation (wk, median & quartiles)	25 (25, 27)	25 (25, 28)	0.45
LA:Ao ratio (mean±SD)	1.68±0.11	1.789±0.04	0.34
Oxygen therapy (d, median & quartiles)	58 (15, 87)	74 (37, 82)	0.08
Assisted ventilation (d, median & quartiles)	58 (15, 67)	65 (37, 82)	0.10
Oxygen therapy at 36 wk post-conceptual age	6 (40%)	25 (55%)	0.46
Assisted ventilation at 36 wk post-conceptual age	5 (33%)	19 (42%)	0.76

successful in closing the PDA in 58 (95%) of the 61 infants. In the early treatment group, PDA closed with indomethacin therapy in all 15 infants, compared to 43 (93%) of 46 infants in the late treatment group. The three infants whose PDA remained opened after two courses of indomethacin had surgical closure of their PDA. In the early treatment group, transient abdominal distension developed in one infant and NEC in three infants after receiving indomethacin. One infant in the late treatment group developed transient abdominal distension.

Indomethacin Therapy

Treatment Regime and Response Rate

Indomethacin is the most widely used prostaglandin synthetase inhibitor for the pharmacological closure of PDA. At Monash Medical Centre, we began to use indomethacin in 1977 in the oral dose of 0.3 mg/kg per dose given twice 24 hours apart.[24] The response to oral or rectal indomethacin therapy is highly variable, with an overall response rate of about 60%.[6] Intravenous indomethacin therapy has a higher and more consistent success rate of about 90% (range 75-96%). Absorption of orally administered indomethacin is relatively poor, and the variability in serum levels is greater with oral compared with intravenous therapy. The rate of PDA closure with indomethacin therapy improved at Monash Medical Centre following the change to the intravenous route.[25] Our recent experience from 2000-2002 reported in this article has shown that treatment failure was confined to therapy after one week of age. It has been shown the poorer response in older infants is the result of pharmacokinetic differences at a greater postnatal age, and a larger dose or an increased number of doses may be required to achieve the same closure rate as in younger infants.[26]

Currently, many NICUs follow the indomethacin regime of 0.2 mg/kg per dose given three times every 8 or 12 hours. A randomised controlled trial (RCT) has reported that prolonged therapy (0.2 mg/kg per day given eight times once a day) resulted in a higher success rate (90% vs 53%), no increase in toxicity, and a lower incidence of CLD (35% vs 68%).[27] A more popular alternative is to use a prolonged low-dose regime (0.1 mg/kg per dose intravenously given six times once a day), which has been shown in a RCT to result in a significantly higher initial closure rate (90% vs 77%), a lower subsequent relapse rate (21% vs 40%) and a lower incidence of renal dysfunction (29% vs 53%).[28] Using this regime at Monash Medical Centre, indomethacin therapy was found to be successful in 90% of infants <1500 g birthweight after the first course with a recurrence rate of 3%.[29] Our recent experience from 2000-2002 reported in this article has shown an overall success rate of 95%.

Adverse Effects of Treatment

The renal blood flow velocity decreases for about two hours,[30] and dilutional hyponatraemia can result from a transient reduction in glomerular filtration rate and free water clearance.[31] Frusemide given with indomethacin can prevent the reduction in urine output without affecting its therapeutic effectiveness,[32] but this is contraindicated in the presence of dehydration.[33] Low-dose dopamine has not been shown to reduce the magnitude of oliguria.[34] Indomethacin is not contraindicated in infants with high serum creatinine and blood urea nitrogen levels, because they are often secondary to poor renal perfusion in infants with PDA and would improve following closure of the PDA with indomethacin therapy. Coagulation defects should be corrected before giving indomethacin, as it impairs synthesis of thromboxane A_2, a potent inducer of platelet aggregation, and causes prolongation of the bleeding time. Indomethacin, though protein bound, does not affect the binding of bilirubin to protein and is safe to use in jaundiced infants.[35] Although it had been suggested that indomethacin predisposes the preterm infant to the development of sepsis,[36] this association has not be observed in other studies.

Gastrointestinal complications are associated with serious morbidity and mortality. A review of the literature had revealed 24 cases of gastrointestinal perforation, six of which were associated with NEC and the remainder were focal perforations with no other obvious pathology.[25] These reported cases had a high mortality rate of 86%. The disturbance in mid-gut perfusion in PDA is known to be exacerbated by indomethacin[37] although this can be minimised with a slow infusion over 30 minutes.[38] A study in infants <1000 g birthweight has shown that when indomethacin was given as a slow infusion, the incidence of bowel perforation and NEC in infants treated for a hsPDA was not significantly different from infants without a hsPDA and not given indomethacin.[29] Our recent experience from 2000-2002 reported in this article has shown that NEC following indomethacin therapy was seen only in the early treatment group (3 of 15 infants or 20%). This finding is similar to that from another study that reported a 20% incidence of NEC with bowel perforation when indomethacin was given during the first 48 hours after birth, but no NEC case was reported in the late treatment group.[39] To avoid NEC with early indomethacin therapy, it has been

suggested that the 0.1 mg/kg doses be discontinued as soon as the PDA has closed (mean cumulative dose at ductal closure was 0.35 mg/kg in that study),[40] or that a continuous but slow infusion of indomethacin (0.004 mg/kg/h) be given until ductal closure.[41]

Indomethacin increases systemic blood pressure[42] but causes a significant reduction in flow velocity in the anterior cerebral artery,[43] which can be minimised with a slow infusion.[44,45] Indomethacin has been shown to improve cerebral autoregulation so that cerebral oxygen metabolism is not compromised even at low cerebral perfusion pressures.[46] A large RCT of early prophylactic indomethacin has reported a reduction in the incidence of PDA and severe periventricular haemorrhage.[47] The latter finding could be explained by the fact that early ductal closure with indomethacin results in improved stability of arterial blood-gases and systemic blood pressure, which predispose to periventricular haemorrhage in preterm infants.[48]

Early versus Late Treatment

Neither natural or synthetic surfactant increases the incidence of PDA,[49,50] but left-to-right ductal shunting occurs earlier within the first week following a more rapid recovery from RDS that results in an increase in pulmonary compliance and a decrease in pulmonary vascular resistance and pulmonary arterial pressure. The role of prophylactic indomethacin following surfactant therapy remains controversial. Although prophylactic treatment has been shown to reduce the incidence of PDA and periventricular haemorrhage, it does not improve short-term respiratory outcome or long-term neurodevelopmental outcome.[47,51,52] A RCT comparing indomethacin therapy started on day three versus day seven in infants with a hsPDA confirmed by echocardiography, has shown no respiratory advantage but rather an increase in major complications such as NEC with early treatment.[53] On the other hand, a hsPDA in extremely preterm infants can lead to serious respiratory, intestinal and neurological morbidities, and a delay in indomethacin therapy needs careful justification.[54]

Decisions on indomethacin therapy for hsPDA in the NICU at Monash Medical Centre during 2000-2002, as reported in this article, were individualised and based on clinical and echocardiographic assessment. This clinical practice is similar to that recommended in an overview of RCTs in the treatment of PDA in preterm infants.[55] Even with this expectant and individualised approach to treatment, we have shown that in the post-surfactant era, almost one half of the extremely preterm infants developed clinical features within the first week that led to a suspicion of a PDA, and one quarter of the infants diagnosed to have a hsPDA had early indomethacin therapy in that first week. The complications experienced with early treatment could possibly be avoided with a different dosing regime, but alternative agents for pharmacological closure of PDA that result in less adverse effects have also been considered.

Alternative Agents

Ibuprofen

This is a non-steroidal anti-inflammatory agent which has been shown to be effective in closing the PDA but without affecting intestinal haemodynamics.[56] It does not have a direct effect on cerebral and renal blood flow velocities, and haemodynamic changes are related to closure of the ductus induced by the drug.[57] Ibuprofen is given intravenously at a dose of 10 mg/kg followed by 5 mg/kg 24 and 48 hours later.[58] A RCT has shown that it is as efficacious as indomethacin and is significantly less likely to induce oliguria.[59] However, this comparison was made with an indomethacin regime of 0.2 mg/kg at 12-hour intervals for three doses, and it is known from another RCT that an indomethacin regime of 0.1 mg/kg at 24-hour intervals for six doses results in a higher ductal closure rate with less renal side effects.[28] Comparison of ibuprofen with this prolonged low-dose indomethacin regime has not been done. Day one prophylactic ibuprofen has been compared in a RCT with later expectant treatment for PDA diagnosed by echocardiography.[60] Unlike when indomethacin was given prophylactically, early ibuprofen did not result in significant adverse effects.

Sulindac

This is a relatively renal-sparing cyclo-oxygenase prostaglandin inhibitor that has comparable anti-inflammatory property and potency to indomethacin. The limited clinical experience with sulindac, given orally at a dose of 3 mg/kg every 12 hours for four doses, suggested that it is as effective as indomethacin in closing PDA but without compromise of the renal function.[61] However, its spectrum of gastrointestinal complications is similar to those described for indomethacin, and one infant was reported to have died from haemorrhagic gastritis following sulindac therapy.[62] Until the question of safety could be adequately addressed, the use of sulindac in the treatment of PDA should remain experimental.

Discussion

Clinically stable infants who do not require oxygen or ventilatory therapy generally do not have a PDA that is haemodynamically significant, and they do well even without treatment. However, the benefits of closing a PDA in infants with significant respiratory disease were first established in the first meta-analysis of RCTs published a decade ago.[63] It showed that indomethacin therapy for asymptomatic PDA results in a significantly shorter duration of oxygen therapy and assisted ventilation and shorter time to regain birthweight. Indomethacin therapy for symptomatic PDA results in a significant improvement in cardiorespiratory status and reduction in mortality rate.

There is however no general agreement among neonatologists on the appropriate timing and indications of indomethacin therapy. The threshold for early indomethacin therapy has progressively been lowered in the post-surfactant era. It has been suggested that all infants <1500 g birthweight who are receiving oxygen and ventilatory therapy should be treated with indomethacin when their PDA becomes clinically apparent and is confirmed with an echocardiogram, even before signs of a large left-to-right shunt and evidence of a hsPDA are present.[64] This recommendation was based on a meta-analysis showing that early treatment compared with delayed treatment beyond one week when symptoms other than a PDA murmur has developed, results in a significant reduction in the duration of assisted ventilation and the incidence of CLD. Some NICUs have extended this clinical protocol to performing a routine echocardiogram within a day after surfactant therapy, and giving indomethacin as pre-symptomatic treatment on ultrasound evidence of PDA alone. Evidence of benefit with this practice remains lacking. There may be a role for prophylactic indomethacin in some preterm infants in some NICUs within a few hours after birth immediately after surfactant therapy and without first doing an echocardiogram,[65] but further RCTs have been recommended to assess more precisely its beneficial and adverse effects on short and long-term outcomes.[66] Most neonatologists have been persuaded by recent RCT evidence[47] that this protocol has less merit than previously claimed. However, the reduced need for surgical closure of PDA with prophylactic indomethacin (five infant avoiding surgery for every 100 infants treated) may be of particular importance in NICUs where infants need to be moved to another centre for surgery.[67]

Our recent experience at Monash Medical Centre from 2000-2002 reported in this article is based on a protocol adopted by most NICUs, that is, for echocardiography to be performed only on a clinical suspicion of PDA, and indomethacin therapy to be given only if the PDA is considered haemodynamically significant, a multifactorial decision based on a combination of clinical features and ultrasound data. However, the data presented suggest that this might not be the optimal practice in the post-surfactant era, and the ideal protocol for the management of PDA that gives the greatest effectiveness and safety in extremely preterm infants requires further study.

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