

ORIGINAL ARTICLE

Effect of early targeted indomethacin on the ductus arteriosus and blood flow to the upper body and brain in the preterm infant

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Objective: To determine if indomethacin given to preterm infants with a large ductus arteriosus (DA) in the first hours of life results in maintained or improved brain and upper body blood (superior vena cava (SVC)) flow.

Study design: A randomised, double blind trial of indomethacin *v* placebo. Echocardiography was performed on 111 infants born at < 30 weeks gestation at 3 and/or 10 hours after birth. Infants were eligible if the DA diameter was > 1.6 mm. Infants were randomised to receive indomethacin 0.2 mg/kg or placebo. Crossover occurred if the DA was still > 1.6 mm. Echocardiography was performed one hour after each treatment.

Results: Seventy (63%) infants had a DA > 1.6 mm, with 35 randomised to receive indomethacin and 35 to receive placebo. At one hour there was no difference in DA constriction (indomethacin –20% *v* placebo –15%), change in SVC flow (–1% *v* –9%), for right ventricular output (RVO). Two hours after indomethacin, 62 infants had uncontrolled observations, at which time significant ductal constriction had occurred. At this time, infants of ≥ 27 weeks gestation had significantly greater increases in SVC flow and RVO than infants of < 27 weeks gestation. Infants with failed ductal constriction had significantly lower initial SVC flow and developed more late grade 3/4 peri/intraventricular haemorrhage (P/IVH). Initial SVC flow, but not ductal constriction, was a significant predictor of late grade 3/4 P/IVH in adjusted analysis.

Conclusions: Indomethacin had minimal effect on ductal constriction and blood flow at one hour compared with placebo. Failure of ductal constriction is associated with low SVC flow and subsequent late severe P/IVH.

One fifth of surviving very premature babies do so with some degree of neurodevelopmental disability¹, and peri/intraventricular haemorrhage (P/IVH) is a major risk factor.² Previous studies suggested that low blood flow to the brain on the first day of life almost always precedes late P/IVH in extremely premature infants.^{3–4} Blood flow to the brain and upper body as measured in the superior vena cava (SVC) usually falls at 5–12 hours of age.⁴ Late P/IVH usually occurs after spontaneous improvement in SVC flow.⁴ These low flows are associated with lack of antenatal steroids, higher mean airway pressures, a larger diameter ductus arteriosus (DA), and higher systemic vascular resistance.^{4–5} Of relevance to this study, the association between low flow and large diameter DA is most significant in the first 6 hours after birth.⁴

Meta-analysis has shown that prophylactic indomethacin given to premature infants reduces the incidence of symptomatic DA and prevents P/IVH.⁶ Despite this, no improvements in neurodevelopmental outcome have been shown.^{6–8} In these trials, indomethacin was given to unselected infants irrespective of DA size. It is widely assumed that the effect of indomethacin in preventing P/IVH is not due to its effect on the DA but to its cerebrovascular effect.^{9–14} The observations noted above led us to question this assumption and to suggest that if we could target indomethacin at babies in whom early postnatal DA constriction has failed, we may be able to optimise the benefits and minimise the harms of indomethacin.

The cardiovascular effect of indomethacin has mostly been studied in preterm infants with a symptomatic DA after the first day of life,^{9–11 15–20} a period when systemic blood flow has

usually improved spontaneously.^{4 21} One uncontrolled study of prophylactic indomethacin at 6 hours of age found reduced cerebral blood flow velocity but unchanged right ventricular output (RVO) 30 minutes after indomethacin.²² Our aim was to examine the short term haemodynamic effect of indomethacin when given in the first few hours after birth selectively to infants in whom early spontaneous postnatal DA constriction had failed. Our hypothesis was that indomethacin given to preterm infants with an early large DA would result in maintained or improved blood flow to the brain and upper body.

METHODS

Study design

The study was a two centre prospective, randomised, double blind study of indomethacin *v* placebo in preterm infants of < 30 weeks gestation with a large DA in the first hours of life. The other treatment was given if there was failure of DA constriction one hour after the initial treatment. The primary outcome was change in SVC flow. The study was carried out in the Royal Prince Alfred Hospital and Royal North Shore Hospital Neonatal Intensive Care Units, Sydney, Australia between October 1998 and September 1999. The ethics committees of Central Sydney and Northern Sydney Area Health Services approved the study.

Abbreviations: P/IVH, peri/intraventricular haemorrhage; SVC, superior vena cava; DA, ductus arteriosus; RVO, right ventricular output

Infants

Infants < 12 hours of age born at < 30 weeks gestation were eligible. They were enrolled in the trial of indomethacin *v* placebo if they were identified as having a large colour Doppler diameter DA (> 1.6 mm) in the first 12 hours of life. This was the median diameter in a previous cohort of infants at 5 hours of age.⁴ Informed consent was obtained antenatally where possible. Infants were excluded if parental consent was refused, a major cerebral haemorrhage (grade 3 or 4) was found on initial head ultrasound, major congenital abnormality or cardiac abnormality was identified, the infant was considered by the attending clinician to be non-viable, or if inotrope or indomethacin had been given previously. No infant was documented as receiving antenatal indomethacin.

Study protocol

Infants enrolled in the study underwent echocardiographic monitoring at 3 hours, 8–10, and 24 hours of age. If a large DA (colour Doppler diameter > 1.6 mm) was identified before 12 hours of age, infants were randomly allocated to receive indomethacin or placebo (vial A) with the other treatment given (vial B) if there was inadequate ductal constriction. Double blinding and randomisation were achieved by preparing individual trial packs comprising two identical looking vials labelled A and B in pharmacy. Indomethacin and placebo were randomly allocated to vial A and B. Vial A was always given first. Infusions were given over 20 minutes. Repeat echocardiography was performed one hour after infusion was completed. Vial B was given if there was inadequate ductal constriction defined as a colour Doppler diameter > 1.6 mm and < 30% constriction from the initial ductal diameter. An additional scan was performed two hours after the final infusion. Infants identified as having low SVC flow (< 41 ml/kg/min) on or after completion of the study protocol received volume (normal saline 10 ml/kg) and inotrope (dobutamine and/or dopamine).

Echocardiographic monitoring

Echocardiography was performed on infants immediately before and one hour after infusion of the contents of vial A and vial B (if given), and two hours after the final infusion. As a result, all 70 infants had placebo controlled observations one hour after infusion of vial A, 53 infants had placebo controlled observations after vial B, and 62 infants had uncontrolled observations two hours after receiving indomethacin. All measurements were performed blind to treatment allocation. An Acuson 128/XP10 ultrasound scanner was used with a 7 MHz vector array transducer incorporating colour flow and pulsed wave Doppler. The scan was recorded on to VHS videotape, and the measurements then taken from the videotape. Structural normality of the heart was established on the initial scan. SVC flow,²¹ ductal diameter, and RVO²³ were measured using techniques described previously.

SVC flow

SVC diameter was measured as it enters the right atrium from the parasternal long axis view. The mean diameter was calculated as the average of the minimum and maximal diameters of three to five cardiac cycles. SVC flow measurements were taken from a low subcostal view with minimal angle of insonation. Pulsed Doppler recordings were made at the junction of the SVC and the right atrium. The Doppler range gate was manipulated in the SVC until the clearest ultrasound velocity spectral displays were obtained. The velocity-time integral for 5–10 consecutive cardiac cycles was measured incorporating both forward and backward SVC

flows, and calculated using Acuson XP10 software. The SVC flow was calculated using the following formula:

$$\text{SVC flow} = (\text{velocity time integral} \times \pi \times (\text{mean SVC diameter}^2/4) \times \text{heart rate})/\text{body weight}.$$

The resulting value was expressed as ml/kg/min. Median intraobserver and interobserver reliability for SVC flows were previously reported as 8% and 14% respectively.²¹

Ductal diameter

The colour Doppler image was obtained from the high left parasternal view. The colour flow Doppler mapping scale was set to the maximal range of the automatic preprocessing, usually 0.64–0.8/ms. The gain was set to optimise the colour flow image within the course of the duct and eliminate any peripheral colour interference. When patent, the minimum diameter (site of maximal constriction) of the colour flow jet within the course of the ductus was measured from a frame by frame analysis of the videotape. End systolic frames with the clearest discrete appearance to the shunt within the duct were used for measurement. A mean was taken from three to five cycles. Previously reported intraobserver reliability of this measurement found a coefficient of variation of 12% between measurements.²⁴

Clinical and physiological data

Oxygen requirements, ventilatory settings, and intra-arterial blood pressures were recorded at the time of each scan. Invasive arterial monitoring using umbilical or peripheral arterial catheters was available in 60 of the 70 infants enrolled. Cerebral ultrasound was performed using a 7 MHz transducer at 3, 8–10, and 24 hours. Any P/IVH was noted and classified according to Papile grading. Routine head ultrasounds were performed between day 4 and 7 and on day 28. Late P/IVH was defined as any P/IVH that was not present on the scan at 3 hours of age.

Sample size and statistical analysis

To detect a difference in change in SVC flow from 47 (24) ml/kg/min (mean (SD) in previous cohort study) to 69 ml/kg/min (mean for normal babies) with 95% confidence and 80% power, 20 babies in each arm (total 40) were required.^{4, 21} Seventy infants were enrolled to allow for uncertainty. Data were analysed as the change in the variable from before to one and two hours after intervention with a PC based statistics package (SPSS for Windows) using the *t* test or Mann-Whitney U test and χ^2 or Fisher exact test where appropriate. Data analysed as “mean % change” represents the mean percentage change for each individual infant. *p* < 0.05 was considered significant. Multivariate linear regression was performed to adjust for any baseline differences in ductal diameter between groups. In the analysis of ductal constriction for prediction of grade 3/4 P/IVH, backward stepwise logistic regression was used to adjust for antenatal risk factors and baseline haemodynamic variables. Variables were incorporated in the model if the direction of effect was stable and they were actual confounders—that is, affected the estimate of effect by more than 10%.

RESULTS

Between October 1998 and September 1999, 138 infants of 23–29 weeks gestation were admitted to the neonatal units. Consent was not obtained or an investigator was not available for 25 (18%) infants. The mean gestation (27.2 *v* 26.9 weeks) and birth weights (1089 *v* 1001 g) of non-enrolled infants were similar to enrolled infants. Two of the

113 infants monitored by echocardiography were excluded because grade 3/or 4 P/IVH was detected on the initial scan.

Seventy of 111 infants (63%) were found to have a DA > 1.6 mm and were randomised to receive indomethacin or placebo. Two infants did not complete the protocol because inotropes were given for hypotension. Significantly more infants with a large DA were < 27 weeks gestation than those infants with a small or no DA (46% v 27%, p = 0.05). The infants with a large DA were more likely to be ventilated (97% v 78%, p = 0.002) and have respiratory distress syndrome (84% v 49%, p < 0.001). Subsequently, they were more likely to have a pulmonary haemorrhage (16% v 2%, p = 0.05). There were no significant differences for any other clinical outcome including mortality, P/IVH, periventricular leucomalacia, and necrotising enterocolitis.

Indomethacin versus placebo after one hour

Thirty five infants were initially randomised to receive indomethacin and 35 to receive placebo at a median age of 4.3 hours (range 2–12); echocardiography was performed one hour later. Sixty of these infants had invasive blood pressure monitoring. Infants randomised to receive indomethacin and placebo were well matched for gestation (26.7 v 26.9 weeks), birth weight (958 v 1002 g), and important antenatal and postnatal variables (table 1). Baseline haemodynamic data for infants randomised initially to receive indomethacin and placebo, including ventilation parameters, size of DA, SVC flow, RVO, and blood pressure, were similar. The clinical outcomes including mortality (26% v 29%), P/IVH (34% v 23%), periventricular leucomalacia, and necrotising enterocolitis were also similar.

Individual responses to indomethacin and placebo can be seen in fig 1. There were no significant differences for mean % change in DA diameter (–20% v –15%) and SVC flows (–3.2 v –10.5 ml/kg/min, p = 0.2) in infants who received indomethacin compared with placebo one hour after infusion (table 2). Adjusting for baseline ductal diameters using multiple linear regression did not change the finding of a non-significant difference in change in SVC flow between the two groups. The response to indomethacin was also not significantly different from placebo for change in mean blood pressures (+1.4 v +0.1 mm Hg, p = 0.3) or RVO

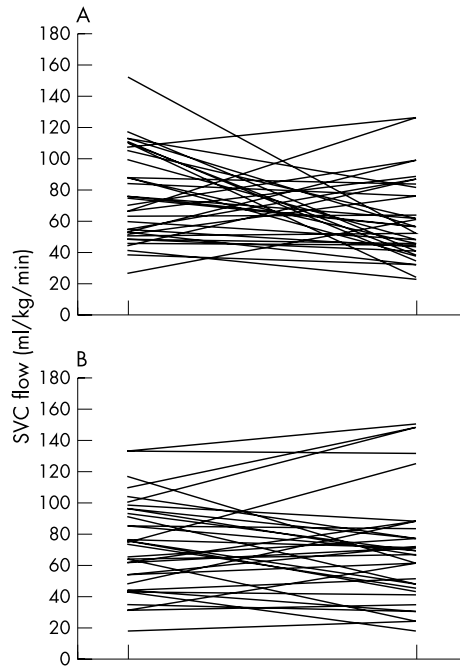


Figure 1 Scatterplots of blood flow in the superior vena cava (SVC) from before to one hour after infusion of placebo (A) or indomethacin (B). n = 35 in each case.

(–8.8 v –1.6 ml/kg/min, p = 0.4). There was a non-significant trend for infants born at 27–29 weeks gestation to maintain SVC flows after indomethacin better than infants born at < 27 weeks gestation (–11.7 v –1.5 ml/kg/min, p = 0.2).

Crossover, indomethacin versus placebo

Fifty three infants with a persistently large DA (> 1.6 mm) and inadequate DA constriction (< 30%) crossed over to the other intervention, 28 to indomethacin and 25 to placebo. Of the 17 infants who did not cross over, nine who received indomethacin and six who received placebo had adequate ductal constriction one hour after the first infusion. One infant who received indomethacin died and one infant who received placebo was withdrawn because of hypotension.

One hour after infusion, there were no significant differences in infants who crossed over to indomethacin or placebo with respect to mean % change in DA diameter (–19% v –20%, p = 0.6), SVC flow (–4.3 v +2.0 ml/kg/min, p = 0.3), or RVO (–5.5 v –20.2 ml/kg/min, p = 0.1). Infants receiving indomethacin after crossover had a significantly

Table 1 Baseline clinical characteristics and physiological data, and subsequent outcomes for infants randomised to receive indomethacin or placebo

	Placebo	Indomethacin	p Value
Gestation (weeks)	26.9 (0.30)	26.7 (0.29)	
Birth weight (g)	1002 (48.8)	958 (43.3)	
Antenatal steroids; any	31 (89%)	34 (97%)	
Caesarean section	20 (57%)	22 (63%)	
RDS	29 (83%)	30 (86%)	
Baseline physiological data			
Mean airway pressure (cm H ₂ O)	8.7 (0.32)	8.7 (0.34)	
Heart rate (beats/min)	145 (2.5)	147 (2.8)	
Mean BP (n = 60)	31.3 (1.01)	30.8 (1.08)	
RVO (ml/kg/min)	188.3 (12.14)	190.7 (11.14)	
DA diameter (mm)	2.4 (0.08)	2.6 (0.10)	
SVC flow (ml/kg/min)	73.3 (5.10)	72.5 (4.92)	
Outcomes			
Death before discharge	10 (29%)	9 (26%)	0.8
P/IVH: any	8 (23%)	12 (34%)	0.3
PVL	0/25 (0%)	3/29 (10%)	0.2
NEC	0 (0%)	3 (9%)	0.2

Values are mean (SEM) (n = 35) unless otherwise indicated. P/IVH, peri/intraventricular haemorrhage; SVC, superior vena cava; DA, ductus arteriosus; RVO, right ventricular output; BP, blood pressure; RDS, respiratory distress syndrome; PVL, periventricular leucomalacia; NEC, necrotising enterocolitis.

Table 2 Response one hour after intervention in infants randomised to receive indomethacin or placebo

	Placebo	Indomethacin	p Value
Mean airway pressure (cm H ₂ O)	–0.3 (0.10)	–0.3 (0.13)	0.9
Heart rate (beats/min)	–2 (1.6)	–4 (2.5)	0.7
Mean BP (mm Hg) (n = 60)	0.1 (0.97)	1.4 (0.82)	0.3
RVO (ml/kg/min)	–1.6 (6.22)	–8.8 (5.37)	0.4
RVO (%)	2 (3.2)	–5 (2.9)	0.1
DA diameter (mm)	–0.4 (0.05)	–0.5 (0.08)	0.1
DA diameter (%)	–15 (2.3)	–20 (3.0)	0.3
SVC flow (ml/kg/min)	–10.5 (4.09)	–3.2 (4.43)	0.2
SVC flow (%)	–9 (5.3)	–1 (6.6)	0.3

Values are mean (SEM) change (n = 35). SVC, superior vena cava; DA, ductus arteriosus; RVO, right ventricular output; BP, blood pressure.

greater increase in mean blood pressure (+2.5 v -0.3 mm Hg, $p = 0.02$).

Non-placebo controlled observations two hours after receiving indomethacin

Sixty two of the 63 infants given indomethacin had an echocardiography scan two hours after indomethacin infusion (table 3). Fifty two of these infants had invasive blood pressure monitoring. In nine infants, the two hour observations were after volume (normal saline 10 ml/kg) was given for low blood flow. As these infants do not affect the results of the analysis, they are included in subsequent analyses.

There was no significant change in mean inspired oxygen or airway pressure two hours after infusion, whereas heart rate decreased and mean blood pressure increased significantly. Mean % change in DA diameter (-35%, range -100% to +55%, $p < 0.001$) and RVO (-16.2 ml/kg/min, $p = 0.001$) decreased significantly, whereas there was little change in SVC flow (-1.8 ml/kg/min, $p = 0.6$).

Infants of 27-29 weeks gestation had a significantly greater reduction in heart rate and increase in SVC flow (+5.2 v -10.4 ml/kg/min, $p = 0.03$) and RVO (+3.0 v -30.2 ml/kg/min, $p = 0.04$) two hours after indomethacin infusion compared with infants of < 27 weeks gestation. There was a significant increase in mean blood pressure in infants of 27-29 weeks gestation, although the difference was not significant when compared with infants of < 27 weeks gestation.

Failure of ductal constriction

Of the cohort of 70 infants, 62 had measurements two hours after indomethacin, one infant had measurements one hour after indomethacin, with the remaining seven having spontaneous ductal constriction after placebo. The median ductal constriction for all 70 infants two hours after the initial measurement was -41% (range -100% to +55%). Infants were dichotomised into those whose ducts constricted $\leq 41\%$ and those with greater than 41% constriction (table 4). The median ductal size after two hours was 1.5 mm. The gestational age and birth weights of infants with failure of ductal constriction were not significantly different. They had similar exposures to antenatal steroids and maternal antihypertensives, and were as likely to have been born by caesarean section compared with infants with greater than the median ductal constriction. Infants with failure of ductal constriction had similar initial ductal diameters but significantly lower initial SVC flow (63.2 v 82.6 ml/kg/min, $p = 0.005$). Not all infants ($n = 60$) had invasive blood pressure measurements, but the initial mean blood pressure was also significantly lower. Subsequently, infants with failure of ductal constriction had a significantly

Table 3 Mean (SEM) change in haemodynamic variables for 62 infants two hours after indomethacin infusion

	Change	p Value
Mean airway pressure (cm H ₂ O)	-0.3 (0.21)	0.2
Heart rate (beats/min)	-6 (1.4)	< 0.001
Mean BP (n=52)	2.1 (0.75)	0.009
RVO (ml/kg/min)	-16.2 (4.53)	0.001
RVO (%)	-7% (2.4)	
DA diameter (mm)	-0.9 (0.07)	< 0.001
DA diameter (%)	-35% (2.8)	
SVC flow (ml/kg/min)	-1.8 (3.65)	0.6
SVC flow (%)	1% (6.1)	

SVC, superior vena cava; DA, ductus arteriosus; RVO, right ventricular output; BP, blood pressure.

Table 4 Baseline clinical characteristics and haemodynamic data, and subsequent outcomes for 70 infants according to whether they had greater or less than the median (41%) ductal constriction two hours after initial observations

	$\leq 41\%$	$> 41\%$	p Value
Gestation (weeks)	26.5 (0.28)	27.1 (0.30)	0.1
Birth weight (g)	946 (39.7)	1014 (51.4)	0.3
Maternal antihypertensives	7 (20%)	10 (29%)	0.4
Antenatal steroids	34 (97%)	31 (89%)	0.4
Caesarean section	21 (60%)	21 (60%)	1.0
RDS	31 (89%)	28 (80%)	0.3
Baseline physiological data			
Mean airway pressure (cm H ₂ O)	8.9 (0.38)	8.6 (0.27)	0.5
Mean BP (mm Hg) (n=60)	28.4 (1.00)	33.6 (0.87)	< 0.001
RVO (ml/kg/min)	177.1 (9.4)	201.9 (77.1)	0.1
DA diameter (mm)	2.5 (0.09)	2.4 (0.09)	0.5
SVC flow (ml/kg/min)	63.2 (4.35)	82.6 (5.07)	0.005
Outcomes			
Low SVC flow 1st 24 hours	18 (51%)	6 (17%)	0.003
Death before discharge	13 (37%)	6 (17%)	0.06
P/IVH: any	11 (31%)	9 (26%)	0.3
Grade 3/4	5 (14%)	1 (3%)	0.2
Early P/IVH	3 (9%)	6 (17%)	0.5
Late P/IVH	8 (23%)	3 (9%)	0.1
Late grade 2/4 P/IVH	6 (15%)	0 (0%)	0.03
Late grade 3/4 P/IVH	5 (14%)	0 (0%)	0.05
PVL	0 (0%)	3 (9%)	0.2
NEC	1 (3%)	2 (6%)	1.0

Values are mean (SEM) (n=35) unless otherwise indicated.

P/IVH, peri/intraventricular haemorrhage; SVC, superior vena cava; DA, ductus arteriosus; RVO, right ventricular output; BP, blood pressure; RDS, respiratory distress syndrome; PVL, periventricular leucomalacia; NEC, necrotising enterocolitis.

higher incidence of low SVC flow in the first 24 hours and, on return of flows, late grade 3/4 P/IVH (14% v 0%). Mortality and rates of early P/IVH and all P/IVH were not significantly different. Initial SVC flow (odds ratio (OR) per 10 ml/kg/min increase 0.36, 95% confidence interval (CI) 0.13 to 0.97, $p = 0.04$), but not ductal constriction (OR per 10% constriction 1.36, 95% CI 0.88 to 2.09) or gestation (OR per week increase 0.63, 95% CI 0.28 to 1.42), remained a significant risk factor for late grade 3/4 P/IVH after adjustment using logistic regression. Analyses were also performed in only those infants who received indomethacin and also by dichotomising infants whose ducts were greater or less than 1.5 mm at two hours after indomethacin. The conclusions are not altered by these analyses. No infant was documented as receiving antenatal indomethacin.

DISCUSSION

This randomised, double blind study found that indomethacin does not have a substantial effect on blood flow to the brain and upper body in infants with a large DA in the first hours of life. It had minimal effect on ductal constriction at one hour when compared with placebo. There were no consistently positive or negative effects on blood flow to the brain and upper body or on RVO. This is reassuring in view of previous uncontrolled observations in the first day of life of a reduction in cerebral blood flow velocity 30 minutes after indomethacin.²² The study does not support our original hypothesis that indomethacin given to premature infants with a large ductus in the first hours of life would result in increased blood flow to the brain and upper body. However, in uncontrolled measurements, significant ductal constriction had occurred two hours after indomethacin. At this time, SVC flow was relatively well maintained when previous data would suggest that it should be falling.⁴ In addition, infants born at 27-29 weeks gestation had significantly higher RVO two hours after indomethacin

infusion than infants born at < 27 weeks gestation, supporting a previous study which found that lower gestation and a large DA were associated with low SVC flow in the first day.⁴ Finally, infants who failed to constrict their ductus after two hours had significantly lower initial SVC flow, were more likely to develop low SVC flow, and subsequently developed significantly more late grade 3/4 P/IVH. After adjustment, initial SVC flow, not ductal constriction, was a significant independent predictor of late grade 3/4 P/IVH. This raises the possibility that, if a large ductus causes P/IVH, it does so through its (negative) effects on cerebral blood flow.

We have previously shown using echocardiographic measurement of SVC flow that almost all infants who have a late grade 2/4 P/IVH have low flow in the first 24 hours of life.⁴ The relation between low cerebral blood flow and subsequent P/IVH is supported by measurements of cerebral blood flow using near infrared spectroscopy.³ These low flows were associated with larger diameter DA and higher systemic vascular resistance.^{4,5} The relation between a large ductus and low flow was greatest in the first hours of life.⁴ Our hypothesis therefore was that closing large ducts in this time period may prevent low systemic blood flow. However, one hour may have been too early for crossover in this study, as significant ductal constriction had not occurred by this time. In addition, our sample size estimation made the assumption that indomethacin would result in a change in SVC flow from the average flow seen in a previous cohort study of similar infants to the mean for normal babies. Clearly this was optimistic given that measurements were taken at a time when SVC flow would be expected to be falling. Future studies of the cardiovascular effects of indomethacin in extremely premature infants should measure effects on blood flow for a longer period and adjust the sample size according to these findings.

The trend for larger preterm infants (born at 27–29 weeks gestation) who had received indomethacin to maintain blood flow more efficiently than more immature infants (< 27 weeks) supports the observation that the benefits of prophylactic indomethacin in preventing P/IVH appear to be greatest in these larger infants.²⁵ Of interest, in the recent large trial of prophylactic indomethacin which showed no improvement in neurodevelopmental outcome, only infants weighing < 1000 g at birth were enrolled.⁷ It is possible that the greatest benefit in closing a large ductus is in the more mature infant.

Indomethacin has multiple effects in preterm infants including closing the ductus⁶ thereby reducing the ductal shunt, increasing systemic vascular resistance,²² and reducing cerebral blood flow in infants with a symptomatic ductus.^{9,10} No previous study has examined the effect of indomethacin on cerebral blood flow in the first day of life. One previous study, which found a reduction in cerebral blood flow velocity at this time, did not measure cerebral blood flow.²² This study suggests that, although using indomethacin to constrict a large ductus does not produce a substantial improvement in blood flow to the brain and upper body, it is maintained at a time when it would be expected to be falling.^{4,21} We speculate that there is a balance between the positive circulatory effect of closing the duct and the negative vasoconstrictor effects. The less mature the myocardium, the more the latter negative effects are likely to dominate.

Infants whose ducts failed to constrict had lower initial blood flows and subsequently developed higher rates of grade 3/4 P/IVH, although after adjustment for baseline SVC flow the effect of the ductus was no longer significant. However, it is also possible that the benefit of using indomethacin to close a large ductus in an immature infant is not manifest by an immediate improvement in systemic blood flow but is evident over a longer time period with better maintenance of

systemic blood flow. The literature and this study do not answer this question. It may also be that the effect of indomethacin in preventing P/IVH is related to its effect in reducing cerebral blood flow during a period of reperfusion,^{9,10} accelerated maturation of the germinal matrix vasculature,¹² or its effect on cerebral autoregulation.^{13,14}

Future studies aimed at preventing P/IVH and improving neurodevelopmental outcome using agents to close the DA should be directed at infants with a large, haemodynamically significant ductus in the first hours of life.^{4,5,26} In view of our observation that low blood flow is related to higher systemic vascular resistance, agents such as ibuprofen may be a better alternative. Ibuprofen appears as effective as indomethacin at closing the ductus^{27–29} and has not been shown to raise systemic vascular resistance or reduce cerebral blood flow in preterm infants with a clinically symptomatic duct.^{30–32}

In conclusion, this study found indomethacin had minimal effect on ductal constriction at one hour when compared with placebo. There were also no consistently positive or negative effects on blood flow to the brain and upper body as measured in the SVC, or in RVO. In uncontrolled observations, significant ductal constriction had occurred after two hours, with more mature infants having significantly greater increases in blood flow than infants born at < 27 weeks gestation. Failure of ductal constriction is associated with low SVC flow and subsequent grade 3/4 P/IVH.

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REFERENCES

- Lorenz JM, Wooliever DE, Jetton JR, *et al*. A quantitative review of mortality and developmental disability in extremely premature newborns. *Arch Pediatr Adolesc Med* 1998;**152**:425–35.
- Vohr BR, Wright LL, Dusick AM, *et al*. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. 2000;**105**:1216–26.
- Meek JH, Tyszczuk L, Elwell CE, *et al*. Low cerebral blood flow is a risk factor for severe intraventricular haemorrhage. *Arch Dis Child Fetal Neonatal Ed* 1999;**81**:F15–18.
- Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F188–94.
- Evans N, Kluckow M. Early ductal shunting and intraventricular haemorrhage in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1996;**75**:F183–6.
- Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants [Cochrane Review]. *Cochrane Library*, Issue 4. Oxford: Update Software, 2002.
- Schmidt B, Davis P, Moddemann D, *et al*. The trial of indomethacin prophylaxis in preterms investigators. long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001;**344**:1966–72.
- Couser RJ, Hoekstra RE, Ferrara TB, *et al*. Neurodevelopmental follow-up at 36 months' corrected age of preterm infants treated with prophylactic indomethacin. *Arch Pediatr Adolesc Med* 2000;**154**:598–602.
- Edwards AD, Wyatt JS, Richardson C, *et al*. Effects of indomethacin on cerebral haemodynamics in very preterm infants. *Lancet* 1990;**335**:1491–5.
- Liem KD, Hopman JC, Kollee LA, *et al*. Effects of repeated indomethacin administration on cerebral oxygenation and haemodynamics in preterm infants: combined near infrared spectrophotometry and Doppler ultrasound study. *Eur J Pediatr* 1994;**153**:504–9.
- Benders MJ, Van de BM, Van Bel F. Doppler sonographic study of the effect of indomethacin on cardiac and pulmonary hemodynamics of the preterm infant. *Eur J Ultrasound* 1999;**9**:107–16.
- Ment LR, Stewart WB, Ardito TA, *et al*. Indomethacin promotes germinal matrix microvessel maturation in the newborn beagle pup. *Stroke* 1992;**23**:1132–7.
- Drayton MR, Skidmore R. Vasoactivity of the major intracranial arteries in newborn infants. *Arch Dis Child* 1987;**62**:236–40.

- 14 **Van Bel F**, Bartelds B, Teitel DF, *et al.* Effect of indomethacin on cerebral blood flow and oxygenation in the normal and ventilated fetal lamb. *Pediatr Res* 1995;**38**:243–50.
- 15 **Hammerman C**, Glaser J, Schimmel MS, *et al.* Continuous versus multiple rapid infusions of indomethacin: effects on cerebral blood flow velocity. *Pediatrics* 1995;**95**:244–8.
- 16 **Kang NS**, Yoo KH, Cheon H, *et al.* Indomethacin treatment decreases renal blood flow velocity in human neonates. *Biol Neonate* 1999;**76**:261–5.
- 17 **Drayton MR**, Skidmore R. Ductus arteriosus blood flow during first 48 hours of life. *Arch Dis Child* 1987;**62**:1030–4.
- 18 **Mardoum R**, Bejar R, Merritt TA, *et al.* Controlled study of the effects of indomethacin on cerebral blood flow velocities in newborn infants. *J Pediatr* 1991;**18**:112–15.
- 19 **Saliba E**, Chantepie A, Autret E, *et al.* Effects of indomethacin on cerebral hemodynamics at rest and during endotracheal suctioning in preterm neonates. *Acta Paediatr Scand* 1991;**80**:611–15.
- 20 **Simko A**, Mardoum R, Merritt TA, *et al.* Effects on cerebral blood flow velocities of slow and rapid infusion of indomethacin. *J Perinatol* 1994;**14**:29–35.
- 21 **Kluckow M**, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F182–7.
- 22 **Yanowitz TD**, Yao AC, Werner JC, *et al.* Effects of prophylactic low-dose indomethacin on hemodynamics in very low birth weight infants. *J Pediatr* 1998;**132**:28–34.
- 23 **Evans N**, Kluckow M. Early determinants of right and left ventricular output in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1996;**74**:F88–94.
- 24 **Kluckow M**, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. *J Pediatr* 1996;**129**:506–12.
- 25 **Clyman RI**. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies [editorial]. *J Pediatr* 1996;**128**:601n7.
- 26 **Evans N**, Iyer P. Assessment of ductus arteriosus shunt in preterm infants supported by mechanical ventilation: effect of interatrial shunting. *J Pediatr* 1994;**125**:778–85.
- 27 **Van Overmeire B**, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. *Arch Dis Child Fetal Neonatal Ed* 1997;**76**:F179–84.
- 28 **Van Overmeire B**, Smets K, Lecoutere D, *et al.* A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *New Engl J Med* 2000;**343**:674–81.
- 29 **Varvarigou A**, Bardin CL, Beharry K, *et al.* Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. *JAMA* 1996;**275**:539–44.
- 30 **Patel J**, Roberts I, Azzopardi D, *et al.* Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. *Pediatr Res* 2000;**47**:36–42.
- 31 **Pezzati M**, Vangi V, Biagiotti R, *et al.* Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. *J Pediatr* 1999;**135**:733–8.
- 32 **Romagnoli C**, De Carolis MP, Papacci P, *et al.* Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates. *Clin Pharmacol Ther* 2000;**67**:676–83.

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