SHORT REPORT

Does patent ductus arteriosus affect feed tolerance in preterm neonates?

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Patent ductus arteriosus (PDA), especially PDA with sepsis, has been reported as a risk factor for feed intolerance in preterm neonates. In this study, the start to full feeds interval was found to be longest in preterm neonates (⩽28 weeks' gestation) with sepsis, followed by that in preterm neonates with sepsis and PDA, and in those with PDA alone.

The difficulties in the definition and interpretation of signs of feed intolerance and the fear of necrotising enterocolitis (NEC) have led to a long list of risk factors for feed intolerance, including sepsis and patent ductus arteriosus (PDA), in preterm neonates. Significant PDA and its treatment with indometacin are known to reduce the mesenteric blood flow.[1] The risk of impaired gut function and translocation of bacteria across the gut mucosa is high in the presence of sepsis.[2] PDA, especially PDA with sepsis, has been reported as a risk factor for feed intolerance in preterm neonates.[3] We aimed to study whether significant PDA, with or without sepsis, is a risk factor for feed intolerance in preterm neonates.

PATIENTS AND METHODS

All preterm neonates (gestation of ⩽28 weeks) born between 1 January 2000 and 30 June 2002, except for those who were outborn, had congenital malformations or died within the first 72 h of life, were included in the study. Neonates were divided into three groups: without PDA, insignificant PDA, and significant PDA, respectively. The diagnosis and management of significant PDA during the study period has been reported earlier.[4] The indometacin regimen was either 100 μg/kg/day for 5 days or 200 μg/kg 12 hourly for three doses at the discretion of the consultant on service. Prophylactic indometacin was not used. Sepsis was defined as bacterial growth on blood culture in presence of the clinical deterioration. The interval between starting and reaching full enteral feeds of 150 ml/kg/day was selected as a marker of feed intolerance. The effect of sepsis on feed intolerance was studied.

Statistical analysis

Univariate analyses included χ^2 and Fisher's exact test for categorical comparisons and Mann–Whitney U and Kruskal–Wallis tests for continuous outcomes. Other tests included Kaplan–Meier probability estimates, with censoring for deaths either before starting feed or full enteral feed, and multivariable analysis using Cox proportional hazards regression modelling.

RESULTS

Outcome measures in 252 neonates were analysed. Compared with other groups, the neonates with significant PDA were less mature (median gestation 25 weeks, quartile range 24–26 weeks) and lighter (median birthweight 745 g, quartile range 623–952 g; table 1). Indometacin was given before starting feed in 46 neonates (43 with significant PDA). The number increased to 83 (78 with significant PDA) by the time full enteral feed was reached. Fourteen neonates (12 with significant PDA) had sepsis before starting feed, and the number increased to 60 (no PDA, 18/124; insignificant PDA, 11/30; significant PDA, 31/91, $p<0.001$) by the time of full enteral feed. Seventeen (8 before full enteral feed and 9 after full enteral feed) neonates developed ⩾stage II NEC. We found no association between significant PDA and NEC. The age at starting feed and full enteral feed was significantly delayed in infants with significant PDA (table 2). Five neonates died before starting feed and 12 did not reach the full enteral feeding stage. The interval between starting feed and full enteral feed ranged between 2 and 69 days, with 50% reaching full enteral feed within 7 days of starting feed. The interval between starting feed and full enteral feed was markedly associated with PDA, sepsis and gestation, and marginally related to intrauterine growth restriction (IUGR). A significant interaction between PDA and sepsis before full enteral feed was evident ($p = 0.002$), and indicated their marked effects in combination on the interval between starting feed and full enteral feed. Controlling for age at starting feed, gestation at birth (hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.02 to 1.23, $p = 0.014$) and IUGR (HR 0.63, 95% CI 0.39 to 1.02, $p = 0.061$), compared with neonates with no or insignificant PDA and no sepsis, all other neonates had a longer interval between starting feed and full enteral feed. Neonates with sepsis alone had the longest interval (HR 0.21, 95% CI 0.12 to 0.37, $p<0.001$) compared with those with both PDA and sepsis (HR 0.38, 95% CI 0.25 to 0.56, $p<0.001$), and with neonates with PDA alone (HR 0.49, 95% CI 0.34 to 0.70, $p<0.001$). Prolonged interval (>7 days) among those reaching full enteral feed ($n = 235$) was observed in 38 of 122 (31%) neonates without any PDA or sepsis, in 15 of 18 (83%) neonates with sepsis alone without any PDA, in 31 of 53 (59%) neonates with significant PDA alone without sepsis, and in 31 of 42 (74%) neonates with PDA and sepsis. Logistic regression adjusting for gestation at birth and age at starting feed showed a significant interaction between PDA and sepsis ($p = 0.030$). Compared with neonates with no or insignificant PDA and no sepsis, all other neonates were more likely to experience a prolonged interval between starting feed and full enteral feed (sepsis alone: odds ratio (OR) 10.40, 95% CI 2.78 to 38.90, $p = 0.001$; significant PDA alone: OR 2.80, 95% CI 1.35 to 5.81, $p = 0.006$; and significant PDA with sepsis: OR 5.15, 95% CI 2.13 to 12.45, $p<0.001$). IUGR was associated with an increased likelihood for the interval >7 days (OR 6.24, 95% CI 1.64 to 23.73, $p = 0.007$).

DISCUSSION

Our findings that significant PDA and sepsis influence the interval between starting feed and full enteral feed in preterm neonates are in accordance with earlier reports.[3 5] Patole *et al*[5]

Abbreviations: IUGR, intrauterine growth restriction; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus

Table 1 Demographic characteristics of the neonates

	Groups			
	No PDA(n = 124)	No significant PDA (n = 30)	Significant PDA (n = 98)	p Value
Gestational age (weeks)*	27.0 (26–28, 23–28)	25.5 (24–27, 23–28)	25.0 (24–26, 22–28)	<0.001
Birth weight (g)*	1053 (846–1166, 500–1475)	778 (668–995, 470–1310)	745 (624–953, 410–1330)	<0.001
Boys (n, %)	64 (52)	15 (50)	48 (49)	0.952
Growth status (n, %)				
SGA	9 (7)	3 (10)	11 (11)	
AGA	103 (83)	25 (83)	82 (84)	0.638
LGA	12 (10)	2 (7)	5 (5)	
Mode of delivery (n, %)				
Vaginal delivery	53 (43)	13 (43)	57 (58)	0.952
C/S	71 (57)	17 (57)	41 (42)	
5-min Apgar score <7 (n, %)	18 (15)	7 (23)	20 (20)	0.341
CRIB score*	2.0 (1–4, 0–14)	4.5 (2–7.3, 1–14)	7.0 (3–9, 1–16)	<0.001
Antenatal steroids (n, %)				
None	18 (15)	1 (3)	17 (17)	
Complete	57 (46)	12 (40)	32 (33)	0.176
Incomplete	35 (28)	12 (40)	38 (39)	
Other combination	14 (11)	5 (17)	11 (11)	
PIH (n, %)	21 (17)	4 (13)	10 (10)	0.351
PPROM (n, %)	70 (57)	15 (50)	26 (27)	<0.001
APH (n, %)	30 (24)	8 (27)	18 (18)	0.466

AGA, appropriate for gestational age; APH, antepartum haemorrhage; CRIB, Clinical Risk Index for Babies; C/S, caesarean; LGA, large for gestational age; PDA, patent ductus arteriosus; PIH, pregnancy-induced hypertension; PPROM, preterm prolonged rupture of membranes; SGA, small for gestational age.
*Variables are expressed as median (interquartile range, range).

reported the results of a clinical trial of prophylactic carboxymethylcellulose in reducing the time to full enteral feed in neonates with <32 weeks' gestation. The only variable showing any independent influence on the time to full enteral feed, irrespective of the allocation to cellulose or placebo, was the presence of a significant PDA. The median (quartile range) time to full enteral feed was significantly longer (7.5 (4.0–13.8 *v* 4 (3.3–6.0) days, p = 0.01) in neonates with significant PDA than in neonates with no PDA.[5] Berseth [3] analysed feeding outcomes in 105 preterm neonates (24–35 weeks' gestation) to determine the incidence and causes of delays in reaching full enteral feed. Feeding intolerance, defined as failure to reach the full enteral feed of 140 ml/kg/day within 10 days of starting feed, occurred in 13 of 46 (28%) neonates with 30–35 weeks' gestation and in 29 of 59 (49%) of those with 24–29 weeks' gestation. Although several factors were associated with delays in reaching full enteral feed, a diagnosis of PDA, or PDA and late-onset sepsis (after day 3), was a major risk factor.[3] Adverse effects of PDA, indometacin and sepsis per se on intestinal perfusion and mucosal integrity as well as their interplay may explain such results.[1 2 6–8] Increasing evidence suggests that nosocomial infections are caused by translocation of enteric organisms.[6] Endotoxaemia and sepsis impair mesenteric perfusion and cause organ dysfunction and exacerbations of polymicrobial bacteraemia owing to intestinal mucosal leakage.[2] Sepsis is reported to increase the risk of late ductal reopening, and failure of PDA closure probably relates to the associated increased levels of prostaglandin and tumour necrosis factor α.[8] Concerns have been raised that indometacin may predispose very low birthweight neonates to sepsis.[9] Considerable biological plausibility thus exists to explain the influence of significant PDA and sepsis on feed tolerance in preterm neonates.

PDA and sepsis are possibly markers of prematurity, and a prolonged interval between starting feed and full enteral feed

Table 2 Nutritional outcomes in neonates

	Group			
	No PDA (n = 124)	No significant PDA (n = 30)	Significant PDA (n = 98)	p Value
Total NBM (days)	2 (1–4, 0–40)	3 (2–6, 1–10)	5 (2–12, 1–59)	<0.001
Total TPN (days)	7 (4–11, 0–272)	10 (6–14, 3–29)	11 (7–20, 0–73)	<0.001
Age at starting feed (days)	3 (2–4, 1–22)	3 (2.5–5, 2–8)	4 (3–7, 1–60)	<0.001
Age at full feed (days)	10 (8–13, 4–24)	12 (9–15, 6–31)	14 (11–20, 6–74)	<0.001
Start–full feed interval (days)*	7 (5–9, 2–27) **n = 122**	7 (6–11, 3–26) **n = 29**	10 (6–14, 4–69) **n = 84**	<0.001
Type of feed (n, %) (n = 247)†				
Breast milk	77 (63)	26 (90)	80 (84)	
Formula	3 (2)	0	1 (1)	0.001
Both	43 (35)	3 (10)	14 (15)	
Time to regain birthweight (days)	13 (10–15, 1–21)	12 (10–15, 1–22)	12 (10–17, 1–30)	0.984

NBM, nil by mouth; PDA, patent ductus arteriosus; TPN, total parenteral nutrition.
Variables are expressed as median, (interquartile range, range) and cases summarised as n (%).
*Excludes deaths before starting feeds; †excludes deaths before reaching feeds.

simply reflects the reluctance to start or continue feeds in the presence of such perceived risk factors for feed intolerance and NEC. In a national survey of Australian neonatologists, 46.4% disagreed that a significant PDA should be closed before initiating feeds.[10] Bellander *et al*[11] has reported that tolerance to early human milk is not compromised by indometacin in preterm neonates with PDA. However, it is difficult to draw clear conclusions, especially in terms of NEC, given their study design and small sample size. The results of a systematic review of observational studies have also raised the possibility that enteral feeding in the presence of significant PDA alone or PDA and sepsis may be related to NEC.[12]

The strong influence of sepsis alone on the interval between starting feed and full enteral feed is not surprising, given its detrimental effects on the gastrointestinal tract.[13] Evidence indicates that the morphological changes and associated altered apoptotic homeostasis may contribute to the increased morbidity, including feed intolerance and NEC, in neonates with IGUR.[14]

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