Blood transfusion and necrotising enterocolitis: a review and survey into feeding practices during transfusion

Studies have identified a temporal association between packed red blood cell transfusion (PRBCT) and necrotising enterocolitis (NEC). Some researchers have suggested that stopping enteral feeds during a PRBCT may reduce the risk of NEC. A survey conducted by the authors in 2011 identified over a third of English neonatal units stopping or reducing feeds around the time of an elective blood transfusion in preterm infants. The evidence for the benefit of this practice is very limited.

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Keywords

blood transfusion; necrotising enterocolitis; enteral feeds

Key points

Power S., Turner C., Sundaram S. Blood transfusion and necrotising enterocolitis: a review and survey into feeding practices during transfusion. *Infant* 2012; 8(1): 10-12.

1. Necrotising enterocolitis remains a significant threat to vulnerable infants.
2. Several studies have reported a temporal association between packed red blood cell transfusion (PRBCT) and necrotising enterocolitis. It is not clear whether this association is causative.
3. Some have recommended a curtailment of enteral feeds during elective PRBCT though there is little evidence to support this practice.
4. The majority of neonatal units in England who responded to the survey in 2011 do not curtail enteral feeds during a PRBCT.

Necrotising enterocolitis (NEC) is a disease familiar to practitioners who care for infants on neonatal units across the world. Published incidence rates vary but recent multicentre studies report rates of 6-7% of all very low birthweight (VLBW) infants[1]. In addition only one study has demonstrated a decline in its incidence over recent times[2]. The disease is of huge impact with mortality rates ranging from 12-30% and prolonged hospital stay noted in survivors[3,4]. It is likely that NEC will remain a significant threat to vulnerable infants for some time into the future.

NEC is primarily a condition of the preterm or VLBW infant, though mature infants can be affected and in one study up to 10% of infants with NEC were term[5]. The classic triad of intestinal ischaemia, pathogenic bacterial colonisation and excess intestinal intra-luminal substrate, was first described by Santulli et al in 1975[6] and still today provides the foundation of our understanding of the pathogenesis of the condition.

In addition to the risk factors listed in **TABLE 1** some researchers have suggested that packed red blood cell transfusion (PRBCT) may also predispose an infant to the development of NEC[7-13].

Prematurity
Aggressive enteral feedings
Patent ductus arteriosus
Indomethacin therapy
Mucosal injury (eg hypoxic-ischaemic insults)
Congenital heart disease
Polycythaemia
Exchange transfusion

TABLE 1 Proposed risk factors for NEC[19-24].

PRBCT as a possible risk factor for NEC

Singh et al[7] performed a retrospective case-controlled study on infants ≤32 weeks' gestational age with NEC between 2000-08 across two North American neonatal intensive care units. They looked at 111 cases of NEC (Bell stage ≥2 – see **TABLE 2**) and compared them with 222 matched controls. They then examined a series of known and proposed risk factors for NEC and compared the findings between index cases and matched controls. Results showed that index cases were significantly more likely to have received a PRBCT 24 hours and 48 hours prior to the diagnosis of NEC (OR 7.6 (2.19-26.4) for 24 hours and 5.55 (1.98-15.59) for 48 hours).

In a retrospective case review El Dib et al[8] studied PRBCT in the 48-72 hours preceding a diagnosis of NEC (Bell stage ≥2) in 25 infants and compared this to 25 matched controls. This was a single-centre study which looked at infants <32 weeks' gestation and with a birth weight <2500g. They found a greater proportion of infants with NEC received a PRBCT in the 48 and 72 hour time periods before diagnosis than did the matched controls (56% *v* 20% p=0.019 48h; 64% *v* 24% p=0.01 72h).

Paul et al[9] have published a retrospective cohort study on all VLBW infants cared for at a single North American neonatal unit between 1993 and 2007. They defined 'NEC after transfusion' as that which occurred within 48 hours of a PRBCT.

They looked at 2311 infants including 122 diagnosed with NEC (Bell Stage ≥2). They found that VLBW infants receiving a PRBCT were more than twice as likely to develop NEC within 48 hours of that transfusion than those who were not transfused (OR: 2.3 (95% CI: 1.2-4.2).

Mally et al[10] reviewed all NEC cases in a single centre over a 17-month period between 1999-2000. They too defined 'transfusion-associated NEC' as cases in which symptoms occurred within 48 hours of PRBCT. Six of 17 cases of NEC were 'transfusion-associated NEC'. These infants were stable, growing, spontaneously breathing infants receiving full enteral feeds prior to the onset of NEC. Other authors have also reported a time-related association between PRBCT and NEC[11-13].

One explanation for this temporal association is that PRBCT is more likely to be given to infants developing NEC but not yet diagnosed with the condition, than it is to those who are not developing the condition. Non-specific symptoms manifested as NEC develops, may encourage practitioners to order transfusions that they would not order in asymptomatic infants. None of the above studies is able to exclude this possibility.

A second explanation of course is that PRBCT increases the risk of NEC in some infants.

Possible effects of PRBCT on development of NEC

A number of mechanisms to explain the association between PRBCT and NEC have been suggested.

Krimmel et al[14] have shown that following PRBCT there is a transient loss of responsiveness in mesenteric blood flow during an enteral feed. They found that following a transfusion there was a blunting of the post-prandial increase in mesenteric blood flow velocity they had identified pre-transfusion. This could lead to a relative intestinal ischaemia which in turn could predispose an infant to develop NEC.

A second hypothesis is that PRBCT stimulates an excessive intestinal immune response[15], similar to transfusion-related lung injury in adults. If this is the case, why the response should be predominantly intestinal is unclear.

A third hypothesis relates to nitric oxide, a potent vasodilator. PRBC are known to have diminished capacity to donate nitric oxide to the endothelium and thus may cause relative intestinal ischaemia[16].

Data on stopping enteral feeds during PRBCT

Enteral feeds are implicated in the aetiology of NEC[17]. If PRBCT is another possible risk factor, then the decision has to be made as to whether to curtail feeds during a transfusion. The evidence to support curtailment is limited.

El Dib et al[8] reported that following the implementation of a policy to withhold all enteral feeds for the duration of a PRBCT in VLBW infants, there was a significant reduction in the incidence of NEC. This is the only study to the authors' knowledge to publish on this specific issue. It is a single centre study and the numbers of infants with NEC (nine before the change and two after) and the short time periods studied (18 months before and after change) mean that in spite of the finding reaching statistical significance, it should be interpreted with caution.

Length of the curtailment – only during the transfusion, or four hours before and four hours after the transfusion – also needs to be considered. Curtailing enteral feeds for the duration of the transfusion alone does not result in an intestine without substrate and therefore may have no impact at all.

To provide definitive data, more appropriately powered trials are necessary yet the numbers that would need to be studied for such a trial to be sufficiently powered may prohibit this ever happening. Questions regarding this practice may remain unanswered for a long time to come.

Stage 1: suspect	Stage 2: confirmed	Stage 3: advanced
■ History of perinatal stress ■ Systemic signs of ill-health: temperature instability, lethargy, apnoea ■ Gastrointestinal manifestations: poor feeding, increased volume of gastric aspirate, vomiting, mild abdominal distension, faecal occult blood (no fissure)	Any feature of Stage 1 plus: ■ Persistent occult or gross intestinal bleeding, marked abdominal distension ■ Abdominal X-ray: intestinal distension, bowel wall oedema, unchanging bowel loops, pneumatosis intestinalis, portal vein gas	Any of the features of Stage 1 or 2 plus: ■ Deterioration in vital signs, evidence of shock or severe sepsis, or marked gastrointestinal haemorrhage ■ Abdominal X-ray shows any of the features of Stage 2 +/- pneumoperitoneum

TABLE 2 Bell Staging criteria for NEC[18].

Current practice regarding stopping enteral feeds during PRBCT

Following a small number of cases of NEC within 48 hours of a PRBCT on the authors' unit, clinicians began to recommend a withholding of enteral feeds for the duration of the transfusion. The authors were keen to evaluate practice across other neonatal units in England.

In March 2011 a postal questionnaire was sent to the lead clinician of each of England's 171 neonatal units. The questionnaire interrogated the unit's practice of enteral feeding when transfusing PRBC, the volume and speed of that transfusion and the presence of written guidance on enteral feeding during transfusion.

A total of 117 responses were received – a response rate of 68%. The response rate was similar across level 1, 2 and 3 units (65%, 69% and 69% respectively). In total 35% of responding units routinely stopped or reduced enteral feeds during PRBCT. Of this 35%, the majority (90%) stopped feeds entirely. The remainder reduced the feed volume without stopping it entirely. When feeds were stopped or reduced, most commonly this was for the duration of the transfusion only (66%) with the remainder of units adjusting feeds for a variable period of time from four hours before to four hours after transfusion.

It is clear from this small study that though there is a lack of consensus regarding enteral feeding during elective PRBCT the majority of clinicians in English neonatal units do not interrupt feeds during these transfusions.

Conclusion

There are a number of reports of a temporal association between PRBCT and NEC in hospitalised preterm infants. Whether this association is causative however is far from clear. For the neonatal practitioner, there is a paucity of evidence to support the withholding of enteral

feeding during a PRBCT. This lack of rigorous evidence is perhaps reflected in the fact that the majority of English neonatal units who responded to the survey in 2011 continue feeds during transfusion.

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