REVIEW

Withholding Feeds and Transfusion-Associated Necrotizing Enterocolitis in Preterm Infants: A Systematic Review

Bonny Jasani,[1,2] Shripada Rao,[1–3] and Sanjay Patole[1,3]

[1]Department of Neonatal Paediatrics, King Edward Memorial Hospital for Women, Perth, Western Australia, Australia; [2]Department of Neonatal Paediatrics, Princess Margaret Hospital for Children, Perth, Western Australia, Australia; and [3]Centre for Neonatal Research and Education, School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia

ABSTRACT

Limited evidence exists to support the withholding of feeds during packed red blood cell (PRBC) transfusion to reduce the incidence of transfusion-associated necrotizing enterocolitis (TANEC) in preterm infants. The aim of the manuscript was to systematically review studies reporting the effect of implementing a policy of withholding feeds on the incidence of TANEC in preterm infants. The following databases were searched for relevant studies published between the databases' inception and December 2016: PubMed, Embase, the Cochrane Central Register of Controlled Trials, the Cumulative Index of Nursing and Allied Health Literature, and Pediatric Academic Societies Abstract Archive. Other relevant sources were also searched. There were no restrictions on study design. Studies reporting on the incidence of TANEC (stage ≥2 necrotizing enterocolitis within 48–72 h) after implementation of a policy of withholding feeds in the peritransfusion period in preterm infants were included. This meta-analysis used a random-effects model with assessment of quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. There were no randomized controlled trials (RCTs). Pooled results from 7 non-RCTs ($n = 7492$) showed that withholding feeds during PRBC transfusion significantly reduced the incidence of TANEC (RR: 0.47; 95% CI: 0.28, 0.80; $P = 0.005$; $I^2 = 11\%$). The overall quality of evidence was moderate on GRADE analysis. These findings suggest that withholding feeds during the peritransfusion period may reduce the risk of TANEC in preterm infants. Adequately powered RCTs are needed to confirm these findings. *Adv Nutr* 2017;8:764–9.

Keywords: enteral feeding, neonates, necrotizing enterocolitis, preterm, transfusion

Introduction

Necrotizing enterocolitis (NEC) leads to significant mortality and morbidity, including long-term neurodevelopmental impairment in preterm infants (1, 2). In 2006, Mally et al. (3) reported the association between NEC and elective packed red blood cell (PRBC) transfusions for anemia of prematurity in preterm infants, which remains an important clinical issue. Mohamed and Shah (4) systematically reviewed the association between PRBC transfusion and NEC [termed transfusion-associated necrotizing enterocolitis (TANEC)]. They concluded that recent exposure to transfusion was associated with NEC, and patients with TANEC were at a higher risk of mortality. Perciaccante and Young (5) compared the incidence of TANEC in 2 epochs. In the first epoch, 7 of 18 cases (38.9%) of NEC occurred within 48 h of a transfusion. In the second epoch (with the change to withholding feeds), none of the cases of NEC occurred within 48 h of a PRBC transfusion. Numerous studies have since assessed the impact of withholding feeds in the peritransfusion period on the incidence of TANEC.

Considering the severity of TANEC, we aimed to systematically review studies reporting the effect of withholding feeds in the peritransfusion period on the incidence of TANEC in preterm infants.

Methods

We followed the Cochrane Handbook of Systematic Reviews of Interventions (6) and the Meta-Analysis of Observational Studies in Epidemiology (7) guidelines. Ethics approval was not required.

Eligibility criteria

Types of studies. Randomized controlled trials (RCTs) and non-RCTs comparing withholding versus continuing feeds during the peritransfusion period were eligible for inclusion. Narrative reviews, systematic reviews, case

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Address correspondence to BJ (e-mail: bonnyjasani@gmail.com).
Abbreviations used: FEM, fixed-effects model; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MBFV, mesenteric blood flow velocity; NEC, necrotizing enterocolitis; PRBC, packed red blood cell; RCT, randomized controlled trial; TANEC, transfusion-associated necrotizing enterocolitis.

reports, letters, editorials, and commentaries were excluded but were read to identify potential additional studies.

Search strategy. The following databases were searched in December 2016: PubMed (http://www.ncbi.nlm.nih.gov, 1966–2016), Embase via Ovid (http://ovidsp.tx.ovid.com, 1980–2016), the Cochrane Central Register of Controlled Trials (http://www.thecochranelibrary.com, through December 2016), the Cumulative Index of Nursing and Allied Health Literature via Ovid (http://ovidsp.tx.ovid.com, 1980 to December 2016), and the Pediatric Academic Societies Abstract Archive (http://www.abstracts2view.com/pasall, 2000–2016). Abstracts from other conference proceedings, such as the Perinatal Society of Australia and New Zealand, the European Academy of Paediatric Societies, and the British Maternal and Fetal Medicine Society, were searched in Embase. The gray literature was searched through the National Technical Information Service (http://www.ntis.gov/), Open Gray (http://www.opengrey.eu/), and Trove (http://trove.nla.gov.au/).

The reference lists of eligible studies and review articles were searched to identify additional studies. Reviewers BJ and SR conducted the literature search independently. No language restrictions were applied. Only published data were used for those studies, where available.

The following terms were used for our database searches: feeding[All Fields] AND ("blood transfusion"[MeSH Terms] OR ("blood"[All Fields] AND "transfusion"[All Fields]) OR "blood transfusion"[All Fields] OR "transfusion"[All Fields]) AND ("necrotising enterocolitis"[All Fields] OR "enterocolitis, necrotizing"[MeSH Terms] OR ("enterocolitis"[All Fields] AND "necrotizing"[All Fields]) OR "necrotizing enterocolitis"[All Fields] OR ("necrotizing"[All Fields] AND "enterocolitis"[All Fields])). No additional studies were identified when the search was repeated using the terms "nutrition support" OR "enteral nutrition."

Study selection. Abstracts of the citations obtained from the initial broad search were read independently by 2 reviewers (BJ and SR) to identify potentially eligible studies. Full-text articles were obtained and assessed for eligibility by 2 reviewers independently (BJ and SR) under the predefined eligibility criteria. Differences in opinion were resolved by group discussion among all reviewers to reach consensus. In the case of multiple publications from the same study, they were considered as a single study and unique data shared in each publication were included where relevant. Care was taken to avoid including duplicate data from such multiple publications.

Data extraction. Reviewers BJ and SR extracted the data independently by using a data collection form designed for this review. Information about the study design and outcomes was verified by all reviewers. Discrepancies during the data extraction process were resolved by discussion and consensus among all reviewers.

Quality of included studies. Quality assessment of the included studies was performed independently by 2 authors (BJ and SP) by using the Newcastle-Ottawa scale. The maximum possible score was 9 stars and the minimum was 0. The Cochrane handbook mentions that the Newcastle-Ottawa scale is difficult to apply; hence, agreement between review authors is likely to be modest. We therefore held regular group discussions to resolve differences of opinion while assessing the quality of the cohort studies. Differences of opinion were resolved by consensus after group discussion involving all authors.

Statistical analysis. For the meta-analysis, forest plots were calculated using weighted scores and a random-effects model (REM). We chose the REM over the fixed-effects model (FEM) because it accounts for variations between studies related to intervention and population characteristics. Results were verified using an FEM. Statistical heterogeneity was assessed with the χ^2 test and the I^2 statistic and by visual inspection of the forest plot (overlap of CIs). A P value <0.1 on the χ^2 statistic was considered to indicate heterogeneity. I^2 values were interpreted according to the guidelines of the Cochrane handbook as follows: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; and 75–100%, considerable heterogeneity (6). All statistical calculations were conducted using Review Manager software (version 5.3.11; The Cochrane Collaboration).

Summary of findings table

Key information about the quality of evidence, the magnitude of the effect of the intervention, and the sum of available data on the main outcome was presented in a summary of findings table according to Grading of Recommendation, Assessment, Development and Evaluation (GRADE) guidelines (8).

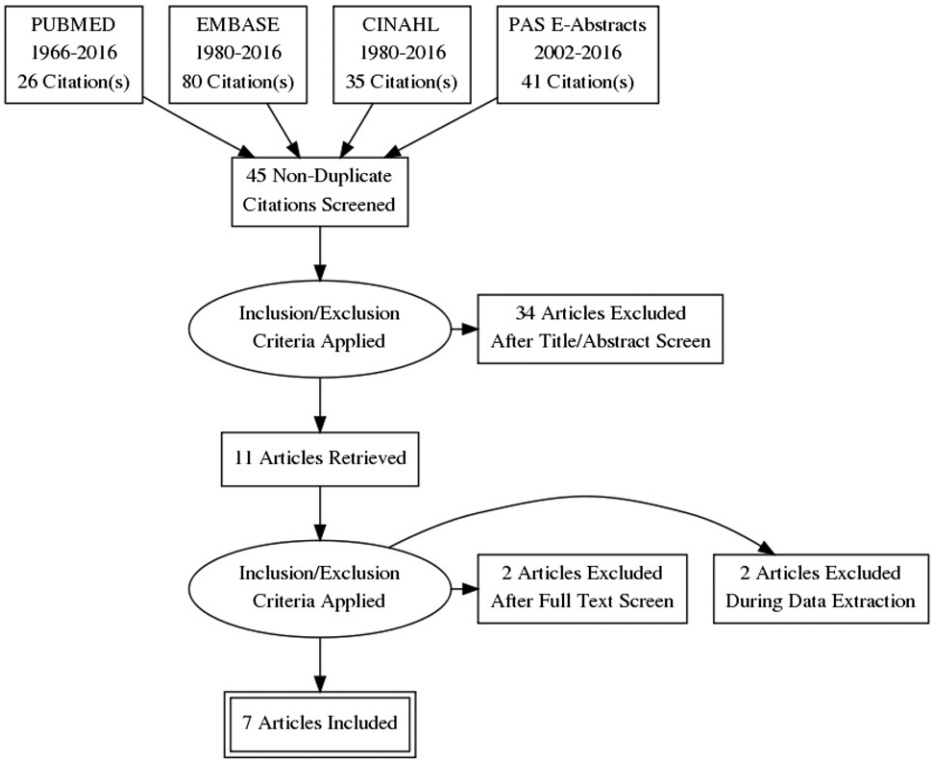

FIGURE 1 Flow diagram of search strategy and study selection. CINAHL, Cumulative Index of Nursing and Allied Health Literature; PAS, Pediatric Academic Societies.

TABLE 1 Characteristics of included studies[1]

Study (reference)	Study population, *n*	NEC stage	TANEC definition (definite NEC <48 h of PRBC transfusion)	Feeding protocol	Preimplementation (epoch 1) TANEC, *n/N*	Postimplementation (epoch 2) TANEC, *n/N*
Perciaccante and Young (5)	595 VLBW infants	≥2	Defined	Cessation of feeds 4 h before, during, and after completion of transfusion	7 of 289	0 of 306
Derienzo et al. (9)	1380 VLBW infants	≥2	Defined	Feeds to be withheld for 4 h before, during, and after transfusion, at which time feeds are restarted at 50% of the original volume for 12 h and then advanced to the original volume	51 of 1065	9 of 315
Meneses et al. (10)	1201 LBW infants	Not mentioned	Defined	Feeds to be withheld 3 h before and 9 h after every RBC transfusion	11 of 628	4 of 573
Mohamed et al. (11)	2422 VLBW infants	≥2	Defined	Not mentioned	20 of 1550	7 of 872
Bajaj et al. (12)	137 infants with a birth weight <1250 g	Not mentioned	Defined as NEC <72 h of PRBC transfusion	Feeds withheld for ≥12 h	1 of 51	2 of 86
Rindone et al. (13)	1577 infants with a gestational age of ≤34 wk	>2	Defined	Feeds withheld for >24 h after transfusion	6 of 835	0 of 742
Doty et al. (14)	108 VLBW infants	≥2 NEC	Defined	Not mentioned	11 of 116	0 of 64

[1] LBW, low birth weight; NEC, necrotizing enterocolitis; PRBC, packed RBC; TANEC, transfusion-associated necrotizing enterocolitis; VLBW, very low birth weight.

TABLE 2 Quality assessment (cohort studies)[1]

	Selection				Comparability	Outcome			
Study (reference)	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Demonstration of outcome of interest not present at start of study	Comparable on basis of design/analysis (maximum score of 2)	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Total score (of 9)
Perciaccante and Young (5)	*	*	*	*	*	*	*	*	8
Derienzo et al. (9)	*	*	*	*	*	*	*	*	8
Meneses et al. (10)	—	—	*	*	*	*	*	*	6
Mohamed et al. (11)	*	*	*	*	*	*	*	*	8
Bajaj et al. (12)	*	*	*	*	*	*	*	*	8
Rindone et al. (13)	—	—	*	*	*	*	*	*	6
Doty et al. (14)	*	*	*	*	*	*	*	*	8

[1] *, score of 1; —, score of 0.

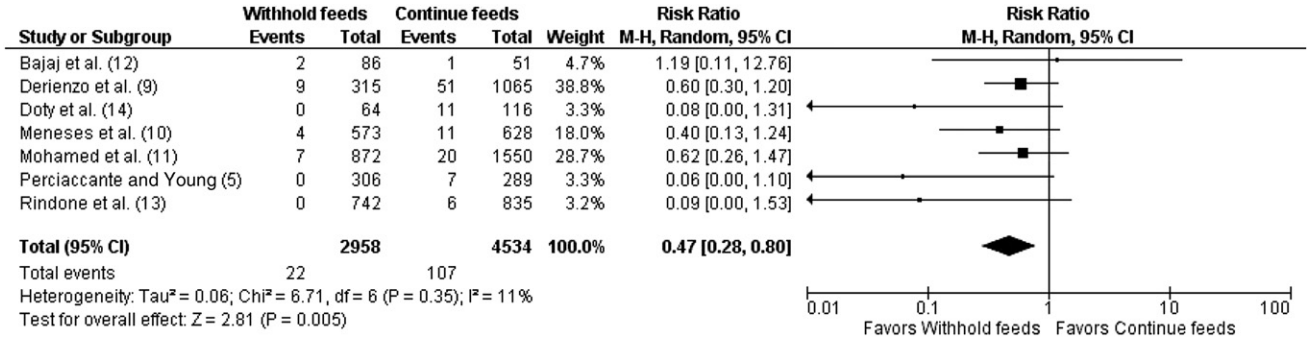

FIGURE 2 Association of withholding feeds peritransfusion and incidence of transfusion-associated necrotizing enterocolitis in preterm infants. M-H, Mantel-Haenszel.

Results

Our literature search revealed 182 potentially eligible studies. After we removed duplicates ($n = 137$) and reviewed the full-text articles, we found 7 studies eligible for inclusion. Details of the selection process are shown in **Figure 1**, and characteristics of the included studies are summarized in **Table 1** (5, 9–14).

Characteristics of included studies

All included studies involved very-low-birth-weight infants, except for studies by Meneses et al. (10) (low-birth-weight infants) and Rindone et al. (13) (≤34 wk of gestation). Bajaj et al. (12) defined TANEC as stage ≥2 NEC occurring within 72 h of PRBC transfusion. Rindone et al. (13) had an extremely conservative peritransfusion feeding policy (feeds were withheld >24 h after PRBC transfusion). All studies reported the incidence of TANEC before and after implementation of a peritransfusion feeding policy.

Quality of included studies

Results of the quality assessment of included studies are reported in **Table 2**. Of a possible score of 9, the majority of studies had scores of 6–8.

Meta-analysis

Meta-analysis via REM of data from 7 studies ($n = 7492$) estimated an RR of 0.47 (95% CI: 0.28, 0.80; $P = 0.005$; $I^2 = 11\%$) (**Figure 2**). Results were similar using the FEM (pooled RR: 0.42; 95% CI: 0.27, 0.66; $P = 0.0001$; $I^2 = 11\%$).

Sensitivity analysis

We conducted a sensitivity analysis by excluding 2 studies that included more mature preterm infants (10, 13). The results continued to show beneficial effects of withholding enteral feeds in the peritransfusion period (RR: 0.51; 95% CI: 0.27, 0.98; $P = 0.04$; $I^2 = 19\%$).

GRADE evidence

Although the results were from observational studies, the evidence was upgraded by 2 steps and deemed as moderate according to the GRADE criteria, owing to the large sample size, narrow CIs around the effect size estimate, the very low P value for the effect size estimate, and mild statistical heterogeneity (**Table 3**).

Discussion

Our systematic review of 7 non-RCTs ($n = 7492$) showed that withholding feeds in the peritransfusion period was associated with a significant decrease in the risk of TANEC in preterm infants.

To our knowledge, few studies have assessed the effect of feeding in the peritransfusion period on mesenteric circulation. Krimmel et al. (15) assessed mesenteric blood flow velocity (MBFV) in 22 preterm infants (25–32 wk of gestation; feeds: ≤60 mL · kg^{-1} · d^{-1}) who required PRBC transfusion for anemia of prematurity. Infants were randomly assigned to continue or stop feeds during the transfusion. Krimmel et al. (15) tested the hypothesis that postprandial hyperemia would not be altered by a PRBC transfusion in preterm infants. In the entire cohort, peak systolic MBFV ($P = 0.02$) and mean MBFV ($P = 0.01$) increased in response to feeding before but not after transfusion in anemic infants. On subgroup analysis, anemic infants weighing >1250 g had increased peak systolic ($P = 0.04$) and mean MBFV ($P = 0.006$) after feeds; no such increase occurred in anemic infants weighing <1250 g. The authors speculated that the

TABLE 3 Summary of findings according to GRADE guidelines[1]

Outcome	Absolute risk, *n* (%)		Relative effect, RR (95% CI)	Participants, *n*	GRADE quality of evidence	Comment
	Estimate without withholding feeds	Corresponding estimate with withholding feeds				
TANEC	107 of 4534 (2.35)	22 of 2958 (0.74)	0.47 (0.28, 0.80), $P = 0.005$	7492	Moderate	See below[2]

[1] GRADE, Grading of Recommendations Assessment, Development and Evaluation; TANEC, transfusion-associated necrotizing enterocolitis.

[2] Although the results were from observational studies, the evidence was upgraded by 2 steps and deemed as moderate, owing to the large sample size, narrow CIs around the effect size estimate, the very low P value for the effect size estimate, and mild statistical heterogeneity.

blunted postprandial hyperemia in infants weighing <1250 g is related to low levels of endogenous nitric oxide and poor nervous system regulation owing to extreme prematurity. Marin et al. (16) used near-infrared spectroscopy to evaluate mesenteric tissue oxygenation in preterm infants (<33 wk of gestation) who were fed versus not fed during PRBC transfusions. Feeding during transfusion was associated with negative trends in postprandial mesenteric oxygenation for ≤15 h after the transfusion. However, withholding feeds during the transfusion was associated with positive mesenteric oxygenation trends during feeds after transfusion. Because TANEC occurs within 48 h after transfusion, these findings suggest that feeding continuation during transfusion could play a role in its development. Marin et al. (16) also reported that infants with a postmenstrual age of <30 wk had a lower baseline regional oxygen saturation at the time of transfusion, suggesting that immature infants with a higher postmenstrual age are at risk of TANEC if feeds are continued during transfusion.

Results of our meta-analysis and studies by Krimmel et al. (15) and Marin et al. (16) suggest that withholding feeds in the peritransfusion period may prevent TANEC by reducing postprandial mesenteric ischemia (17, 18). The strengths of our meta-analysis include its robust methodology, large sample size (7 studies, n = 7492), consistent results across included studies, and minimal heterogeneity (I^2: 11%). Limitations include the fact that all studies were non-RCTs with lack of adjustment for confounders.

There are arguments in favor of (19) and against (20) the value of observational studies in guiding treatment decisions. Experts caution that even large well-conducted observational studies have frequently been shown to be wrong (21). Similarly, some experts caution that pooling of studies in meta-analysis of observational research leads to spurious results (22), whereas others suggest that the advantages of including observational studies in a meta-analysis outweigh the disadvantages (23). Readers must take these concerns and controversies regarding observational studies into consideration when they interpret the results of our meta-analysis. Our literature search revealed an ongoing single-center RCT (clinicaltrials.gov NCT02132819) (24) investigating the effect of withholding feeds during transfusion on the development of transfusion-related acute gut injury in preterm infants. Given its small sample size (n = 150), the results of this trial may not add significant knowledge to the field.

In summary, our results indicate that withholding feeds in the peritransfusion period reduces the incidence of TANEC in preterm infants. Given the limitations of the studies included in our meta-analysis, adequately powered RCTs are needed to confirm these findings. The difficulties in conducting such trials include the low frequency of TANEC, the inability to blind the intervention, and the fact that the existence of TANEC itself has been questioned by experts (25). Furthermore, the effective duration of withholding feeds for protection from TANEC is also not well defined. Pending further research, judging whether the potential benefits of preventing a potentially devastating condition such as TANEC (4) outweigh the consequences of iatrogenic nutritional deprivation for 12–24 h will depend on interpretation of the current evidence by individual clinicians.

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