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Should we believe in transfusion-associated enterocolitis? Applying a GRADE to the literature

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ABSTRACT

Numerous observational studies appear to demonstrate an association between packed red blood cell (pRBC) transfusions and necrotizing enterocolitis (NEC). However, the limited numbers of randomized controlled trials (RCTs) do not support a causal relationship between pRBC transfusion and NEC. We sought to determine the quality of the evidence behind transfusion-associated necrotizing enterocolitis (TANEC), and to formulate a GRADE-based recommendation regarding transfusion practices to reduce the risk of TANEC. A systematic search including MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials and clinical trials registries was performed for studies assessing the association between transfusion and NEC. Teams of two paired reviewers independently screened studies for eligibility, assessed risk of bias using the GRADE framework, and collected data from each eligible study. We examined studies for two time points following transfusion: within 48 h if this was available, and otherwise at any time after transfusion. In total, 23 observational studies and three RCTs met inclusion criteria. The average rating for the quality of evidence of individual studies was between "very low" and "low." On pooling studies for GRADE review, we observed an inconsistency of results. This led to a final overall quality of "very low" for the evidence for an association between transfusions and necrotizing enterocolitis. The pooled outcome of NEC for observational/case control studies was an odds ratio of 1.13 (95% CI: 0.99–1.29) when TANEC was defined as occurring within 48 hours of transfusion. For NEC occurring at any time post-transfusion, the pooled OR was 1.95 (1.60–2.38). Conversely, the pooled outcome of NEC for the RCT data had an odds ratio of 0.6 (0.3, 1.21) with NEC being less frequent in the liberal transfusion group compared to the restrictive transfusion group. The overall quality of the

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; pRBC, packed red blood cell; RCT, randomized controlled trial; TANEC, transfusion-associated necrotizing enterocolitis

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evidence for TANEC is "very low," suggesting very little confidence in the effect estimate. RCT data tended toward apparent protection against NEC. The available evidence is not sufficient to support a practice recommendation around pRBC transfusions in the context of preventing the development of NEC.

Introduction

Neonatal intensive care unit (NICU) patients are among the most transfused populations, but the risks and benefits of this treatment remain unclear. One controversial issue in blood transfusion safety is the validity of an association between packed red blood cell (pRBC) transfusion and necrotizing enterocolitis (NEC). More than 25 years ago, an evaluation of a NEC epidemic in a single-center NICU identified red blood cell transfusions as a potential risk factor.[1] Since then, the majority of numerous observational (cohort and case–control) studies have demonstrated such an association.[2] A majority of clinicians believe that Transfusion-associated NEC (TANEC) exists as a distinct entity,[3] and thus some institutions have adopted policies aimed at its prevention. However, three randomized controlled trials (RCTs) performed to date comparing liberal versus restrictive pRBC transfusion parameters do not support a causal relationship between frequency of transfusions and NEC.[4]

The discrepancy between the experimental and observational bodies of evidence is stark. Hence, the possibility must be considered that the contrast is related to the presence of confounding factors in the observational literature. Given the devastating consequences of NEC, and the potential impact of transfusion on long-term outcome, it is paramount that clinicians be provided an accurate assessment of the associated risks and benefits. Our objective in this review is to determine the quality of the evidence behind the existence of TANEC, and to gauge the strength of recommendations for its prevention, using an explicit GRADE approach.

Methods

GRADE framework

We applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. This widely used methodology provides a clear and comprehensive approach to rate and summarize the quality of evidence behind clinical practices.[5] GRADE rates the quality of evidence as either high, moderate, low, or very low.[6] Observational studies start with a low quality rating, and RCTs start with a high quality rating. Studies may then be graded upward in the following circumstances: for a large magnitude of effect, evidence of a dose–response relation, or when all plausible confounders are accounted for and would likely reduce an apparent effect. Conversely, studies may be graded downward for study limitations, including risk of bias, indirectness or imprecision.[6] The resultant GRADE recommendations reflect reviewers' confidence in the overall estimate of effect, with a rating of "high" suggesting that "further research is very unlikely to change" this confidence and a rating of "very low" expressing that "any estimate of effect is very uncertain."[6]

Systematic review

We set out to answer the question of whether the intervention of pRBC transfusions versus no pRBC transfusions increased the outcome of NEC in the NICU population over all available studies to date.

We followed the standards set by the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[7]

Eligibility criteria

We included full-length RCTs, cohort studies, and case–control studies that evaluated the relationship between blood transfusion and the development of NEC. In most studies selected for inclusion, the criteria for NEC were described as Bell's criteria 2 or greater.

Literature search

We searched MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials, and clinical trials registries (clinicaltrials.gov; controlled-trials.com; who.int/ictrp) using the terms TRANSFUSION and INFANT and NECROTIZING ENTEROCOLITIS. Search results were from inception through January 2016. In addition we searched the abstract archives of the annual meetings of the Pediatric Academic Societies (2002–2014), bibliographies, and personal files. Non-English articles were excluded.

Data collection

The following information was collected from each eligible study:

- *General study characteristics*: author name, year of publication, total number of patients included, and single versus multi-center involvement.
- *Patient characteristics*: description of patient population, including birth weight, and gestational age criteria.
- *Interventions*: details of blood transfusions, including transfusion guidelines when provided.
- *Outcomes*: the definition of NEC, the time interval documented between blood transfusion and NEC.