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PII: S0887-7963(21)00024-9
DOI: https://doi.org/10.1016/j.tmrv.2021.06.003
Reference: YTMRV 50657

To appear in: *Transfusion Medicine Reviews*

Please cite this article as: Carmel Maria Moore , Anna E Curley , Neonatal platelet transfusions: starting again, *Transfusion Medicine Reviews* (2021), doi: https://doi.org/10.1016/j.tmrv.2021.06.003

Neonatal platelet transfusions: starting again

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Highlights

- Preterm prophylactic platelet transfusion does not reduce bleeding.
- Recent evidence suggests harm with higher transfusion thresholds.
- Future research into etiology of harm is necessary.

Abstract

Preterm neonates with severe thrombocytopenia are frequently prescribed prophylactic platelet transfusions despite no evidence of benefit. Neonatal platelet transfusion practice varies, both nationally and internationally. Volumes and rates of transfusion in neonatology are based on historic precedent and lack an evidence base. The etiology of harm from platelet transfusions is poorly understood. Neonates are expected to be the longest surviving recipients of blood produce transfusions, and so avoiding transfusion associated harm is critical in this cohort. This article reviews the evidence for and against platelet transfusion in the neonate and identifies areas of future potential neonatal platelet transfusion research.

Keywords: Infant, newborn; Platelet transfusion; Infant, premature; Thrombocytopenia.

Introduction

There have been many comprehensive review articles about neonatal thrombocytopenia and platelet transfusion over the last two decades.[1-12] These have largely focused on the incidence of thrombocytopenia; etiology, platelet function, potential association of thrombocytopenia and bleeding, prediction of babies most likely to bleed and the potential benefit of platelet transfusions to reduce bleeding events in particular intraventricular hemorrhage. Considerable variation remains in neonatal platelet transfusion practice.[13] Neonatologists, particularly in the US, have appeared to be adopting a more liberal, rather than less liberal, approach to platelet transfusion over time[14, 15] with many clinicians

prophylactically transfusing platelets at levels above $50x10^9$/L. This liberalization of transfusion has occurred despite systematic reviews failing to show benefit of transfusion[16] or correlation of level of thrombocytopenia with likelihood of bleeding.[10]

This liberal approach to platelet transfusion contrasts with a change in general neonatal practice, as neonatologists have embraced less invasive modalities for overall intensive care management including increased use of non-invasive ventilation[17] and less invasive surfactant[18] in extremely preterm infants. At the same time, increased use of infection care bundles in neonatal units worldwide has led to significant reductions in severe sepsis[19]; one of the main conditions causing severe thrombocytopenia in preterm babies. Currently referenced incidences of neonatal thrombocytopenia may therefore not reflect current rates of thrombocytopenia as much neonatal thrombocytopenia is caused by *in utero* growth restriction, sepsis or necrotizing enterocolitis.[20] Over a decade (2009-2019) early onset sepsis reduced from a median incidence of 1.4% to almost 0%, late-onset sepsis reduced from 6.8% vs 5.3% VON and the incidence of necrotizing enterocolitis (NEC) reduced from 6% to 3.3% of very low birth weight (VLBW) babies (birth weight < 1500g).[21]

In addition to background changes in neonatal clinical practice, the publication of the **Pla**telets for **Ne**onatal **T**ransfusion/**Ma**naging **T**hrombocyte transfusions **I**n a **S**pecial **S**ubgroup: Neonates (PlaNeT-2/MATISSE) study[22] in 2019, a neonatal randomized prophylactic platelet transfusion threshold trial, raised many questions about preterm neonatal platelet transfusion practice when it demonstrated increased harm in the form of mortality and major bleed in babies in the more liberal transfusion arm. Although the potential for harm had been suggested over a decade prior to this[3, 23] the retrospective non-randomized nature of these studies prevented significant impact on clinical practice.

What motivates neonatologists to give babies platelet transfusions?

As outlined comprehensively in previous reviews, there is no clear association between thrombocytopenia and bleeding.[10] Similarly, there is no evidence for benefit of prophylactic platelet transfusions. Despite this, clinicians continue to prescribe platelet transfusions in non-bleeding preterm infants, presumably in an attempt to reduce bleeding in

an at-risk population. There is also, no doubt, concern that a failure to transfuse will increase clinical and medicolegal liability in the event of a bleed. Despite significant progress in neonatal care over the past few decades and improved survival of premature infants, extreme prematurity continues to be associated with long term neurodevelopmental, visual, and hearing impairment. There is a high risk of death and major brain injury at early gestations. Nearly seven percent of VLBW infants will have cerebral palsy[24] and 25-50% will have cognitive or behavioral deficits.[25] VLBW infants also have high rates of dysfunction in other cognitive areas such as attention, visual processing, academic progress and executive function. Three out of four babies born weighing less than 750 g will have school difficulties even if they have no neurosensory impairment and normal intelligence.[26] As a result many neonatologists are very focused on prevention of complications known to affect survival and long term neurodevelopment such as intraventricular hemorrhage (IVH), one of the commonest causes of hemorrhage in preterm infants.[27] Severe IVH is associated with a high probability of death or disability, with grade III hemorrhage predicting cerebral palsy (CP) in 26% (95% CI 13-45%) and grade IV predicting abnormal neurodevelopmental outcome in 47% (95% CI 31-64%).[28] Despite changes in neonatal care and prophylactic platelet transfusion practice, the incidence of intraventricular hemorrhage has stayed the same however over the last decade (median incidence any IVH 22%, severe IVH (grade 3 or grade 4) 6.5% vs 6.8% 2009 vs 2019)[21] which might have prompted neonatologists to consider whether prophylactic platelet transfusions were playing a useful role in prevention

What evidence do neonatologists have to guide platelet transfusion?

Until recently, the only evidence neonatologists had to support or refute prophylactic platelet transfusion in the preterm neonate was a single randomized controlled trial from 1993 and a series of retrospective cohort analyses.[3, 29] In 1993, a randomized controlled trial by Andrew et al[29] in 152 VLBW babies, demonstrated that prophylactic platelet transfusion to maintain a platelet count greater than $150x10^9$/L compared to $50x10^9$/L did not reduce the incidence or severity of all categories new onset IVH in preterm neonates. Of note, the rate of new major IVH was increased in the higher threshold group but numbers were too small (12 grade III or IV in the higher threshold vs 5 in the lower threshold) to assess if this was a chance effect.

Since 1993 many of the studies of platelet transfusion in preterm infants have been observational and retrospective. In 2005, Kenton et al demonstrated platelet transfusions were not associated with improvement in mortality or morbidity (short bowel syndrome or cholestasis) in neonates with NEC.[23] Babies who had received higher number and volume of platelets had higher morbidity but it was not possible to determine whether this reflected background severity of illness or effect of platelet transfusions. In 2007 Baer et al[3] retrospectively reviewed 1600 thrombocytopenic babies in the NICU and reported that for all levels of platelet count, babies that received platelet transfusions had a higher mortality rate. Sensitivity analysis of the study suggested that transfusions themselves were likely responsible for some of this harm.[3] Further analysis by the same group in 2009 of babies with platelet counts $<50x10^9$/L showed mortality was not predicted by lowest platelet count but by number of platelet transfusions.[30] Hemorrhages were also not predicted by the lowest platelet count. Major IVH occurred in 20% of babies who had received >10 platelet transfusions compared to 4% in babies who received none.

A 2014 structured review assessed the association between platelet transfusion and bleeding in various patient groups including neonates in the NICU, however the researchers did not distinguish between major and minor bleeds and did not assess the relationship between platelet count and bleeding or take into account temporal ambiguity or timing of the thrombocytopenia in relation to the bleed.[31] Their findings demonstrated the lack of clear evidence in this field and concluded that for critically ill preterm neonates with severe thrombocytopenia and no evidence of bleeding, there was insufficient evidence to make a recommendation for or against platelet transfusion.

In 2019, a further systematic review by Fustolo-Gunnink et al[16] included 30 studies assessing platelet count and bleeding. There were significant methodological limitations to the data assessed: only four showed clear temporal relationships between thrombocytopenia and bleeding, of which two suggested thrombocytopenia was associated with pulmonary hemorrhage and two suggested that platelet count was not associated with any type of bleeding including pulmonary hemorrhage. Three studies assessed the association between platelet transfusion and bleeding but none demonstrated association of platelet transfusion with reduced bleeding risk. The authors concluded prophylactic platelet transfusions might not reduce bleeding risk in preterm neonates.

The PlaNeT-2/MATISSE study was the first randomized trial of platelet transfusion thresholds in current use to prevent bleeding in neonates.[22] There were 660 infants recruited with a median gestational age of 26.6 weeks in the UK, Ireland and The Netherlands. The primary outcome was a composite of death or major bleeding, quantified with the use of a validated neonatal bleeding assessment tool.[32] The study demonstrated that a higher threshold for prophylactic platelet transfusion: $<50x10^9$/L versus $<25x10^9$/L showed increased composite outcome of death and/or major bleeding within 28 days of randomization (26% versus 19%, OR 1.57, 95% CI 1.06-2.32). The study also demonstrated a higher incidence of bronchopulmonary dysplasia in babies transfused at the higher threshold (63% v 54%, 95% OR 1.57, 95% CI 1.06-2.32). There was no difference in necrotizing enterocolitis (NEC) or sepsis.

In 2019, Kumar et al published their study which randomized preterm thrombocytopenic neonates to liberal platelet transfusion (to maintain platelet count >100x10^9/L) or standard treatment (to maintain platelet count >20 x10^9/L).[33] The trial used platelet volumes greatly in excess of those used in routine practice and babies with platelets <50x10^9/L were given a minimum of 40 mL/kg of platelets. Although the primary outcome of interest was patent ductus arteriosus closure, the study noted a significantly higher rate of IVH in the liberally-transfused group: 41% of infants had any grade of IVH in the liberal transfusion group compared with 4.5% in the restrictive group. They also noted a 4.3% increase in IVH for every extra 1 mL/kg volume of platelets transfused. See Table 1.

Authors	Year	Population		Intervention	Control	Primary Outcome	Transfusion/bleeding outcomes	Clinical outcomes	Results
Andrew et al	1993	Birth weight 500-1500g, gestational age <33 weeks, platelet count <150 x 10^9/L first 72 hours, no major bleeding	N=152	Prophylactic platelet transfusion at threshold of <150x10^9/L	Prophylactic platelet transfusion at threshold of <50x10^9/L	Incidence or extension of IVH	Amount of blood product support administered, bleeding time, IVH		**New or extended IVH:** 28% (22/78) vs 26% (19/74) intervention vs control (p = 0.73).
Curley et al	2019	Gestational age <34 weeks, a platelet count of <50x10^9/l, no major bleeding within 72 hours of randomization	N=660	Prophylactic platelet transfusion at threshold of <25x10^9/l	Prophylactic platelet transfusion at threshold of <50x10^9/L	Death or major bleed	Number of platelet transfusions, major and minor bleeding (IVH, pulmonary hemorrhage, frank rectal bleeding, and severe bleeding (fatal, life-threatening, or requiring fluid boluses or red- cell transfusion) transfusion-related adverse events.	Chronic lung disease, new sepsis, new necrotizing enterocolitis Neurodevelopmental outcome at 2 years	**Death/major bleeding:** 1% (85/324) vs 19% (61/329) intervention (odds ratio, 1.57; 95% CI 1.06 to 2.32; P=0.02).
Kumar et al	2019	<35 weeks' gestation neonates with PDA detected <14 days of postnatal age, receiving NSAID	N=44	Prophylactic platelet transfusion at threshold of <100x10^9/L	Prophylactic platelet transfusion at threshold of <20x10^9/L	Time to PDA closure	Cumulative volume of platelet concentrate received within the study period, clinical bleeds (any visible fresh oral, nasal, endotracheal,	PDA closure	**Median time to PDA closure:** 72 hours in both groups (unadj hazard ratio 0.88 [95% CI 0.4–1.9]; P = .697). **IVH:** liberal

		treatment for PDA					gastrointestinal, or skin bleed), new-onset IVH of any grade and grades III and IV IVH, mortality		transfusion group, 40.9% (9/22) vs 9.1% (2/22) restrictive group (P = .034).

Table 1: Randomised controlled trials of platelet transfusion.

What are the limitations of the more recent randomized controlled trials which could help plan future research?

What is the relevance of Andrew's study to current practice? Although a landmark study in its time, a current problem with the study by Andrew et al[29] is that it reflects neonatal practice from several decades ago using higher transfusion thresholds ($150x10^9$/L) and potentially a different cohort of babies with higher median gestational age and birth weight by comparison to the PlaNeT-2/MATISSE[22] study (900g vs 740g) and a lower overall mortality rate (17.8%). The group was not large enough to determine whether there was a significant difference in severe IVH rather than all grades IVH between groups. There was also no long-term follow up of the cohort in terms of neurodevelopmental outcome.

The study of platelet transfusion to promote PDA closure by Kumar et al[33] was useful and in relation to the publication of the PlaNeT-2/MATISSE study timely in its findings. The ductus arteriosus connects the pulmonary artery to the aorta in the fetus, but should close postnatally when pulmonary circulation is established. Morbidity may be associated with a patent ductus arteriosis,[34] however controversy remains about whether or not treatment of PDA is beneficial.[35] The randomized trial of platelet transfusion performed by Kumar et al[33] was based on their prior finding that platelet count less than $100x10^9$/L predicted delayed ductal closure and was associated with a hemodynamically significant PDA. The authors speculated that giving platelets would expedite ductal closure by facilitating clot formation. They included preterm babies less than 35 weeks gestation at birth who had an echocardiographically hemodynamically significant PDA and co-existent thrombocytopenia with platelets $<100x10^9$/L. Their sample size was calculated based on PDA closure as a primary outcome (not IVH) however any grade of IVH, or new finding of more severe grade 3 or 4 IVH within 120 hours of randomization were pre-defined secondary outcomes.

The study was small consisting of only 44 babies. All babies were treated with a non-steroidal anti-inflammatory agent to try to close the PDA in addition to platelet transfusion. Although bleeding was only recorded for 120 hours after the study intervention occurred, mortality at any time during hospital stay was included. The study did not appear to use a validated bleeding assessment tool but did report visible bleeding from mouth, nose, ET, GI or skin in addition to IVH. The volumes given in Kumar et al's study depended on the pre-transfusion platelet count. If the platelets were less than $50x10^9$/L, two back to back transfusions of 15mls per kg per transfusion were given. The authors speculated that there was little chance that the platelets would increase to >$100x10^9$/L with a single transfusion. As a result, babies in the study received a median of 30mls/kg and babies with platelets <$50x10^9$/L received 30mls/Kg in two transfusions presumably over a short period of time (duration of infusion not stated in the trial protocol or article).

The incidental finding of increased IVH is potentially useful because it may indicate that a hemodynamic cause for increased IVH is more likely in the setting of high or rapid volumes of transfusion. The study, although differing in purpose of intervention, did parallel the trend in results seen in the trial by Andrews et al[29] showing an increase in severe IVH. Probably due to the size of the study several important neonatal outcomes were not predefined in the study by Kumar et al such as NEC or BPD.[36] As preterm babies often have significant acute and chronic inflammatory lung disease related to preterm lung structure, volutrauma and hyperoxia there is potential for significant platelet induced inflammatory lung injury. Overall, despite the obvious limitations of design and study size the study may help us determine potential mechanism of harm noted in the larger PlaNeT-2/MATISSE[22] study.

PlaNeT-2/MATISSE study

The PlaNeT-2/MATISSE study[22] was the first randomized trial since 1993 to randomly assign platelet transfusion thresholds in preterm infants. It demonstrated an increased rate of death or major bleeding in babies assigned to a higher platelet transfusion threshold (>$50x10^9$/L). A significant strength of the study was its size; recruiting 660 infants making it the largest neonatal platelet transfusion trial to date. The actual incidence of mortality or major bleed recorded in the trial was higher than the protocol predicted incidence, indicating the study was likely to have been adequately powered and also showing that investigators

were unlikely to have shown systemic consenting bias towards less sick babies. The trial included babies (37%) with early (defined as <5 days for the purpose of the study) and late (63%) thrombocytopenia. Early thrombocytopenia is often associated with placental insufficiency and *in utero* growth restriction. It tends to be self-resolving and values normalize by 7-10 days on average.[37] Despite its more 'benign' nature, neonatologists often transfuse babies with early thrombocytopenia in an attempt to 'prevent' IVH as 95% of IVH occurs in the first 72 hours of life.[38] Late thrombocytopenia is typically related to NEC or sepsis and platelets show increased rates of consumption.[39] Although neonatologists would probably argue against exclusion of either cohort it did lead to a heterogeneous group of infants and with only 37% of babies showing early thrombocytopenia, this study may not be sufficient to deter early platelet transfusion in this group.

The study team developed a bleeding assessment tool for use in the study and validated it internationally.[32] Prospective collection of bleeding data was a significant strength of the study. The classification of rectal bleeding was difficult and the study team chose a pragmatic definition of visible blood per rectum. Delineating rectal bleeding events was difficult however but reassuringly when rectal bleeding was excluded from analysis the primary outcome remained significant. In terms of cerebral bleeds, dilatation of cerebral ventricles <1 week after bleed was considered a bleed extension (severe bleed) but if it occurred ≥1 week was considered post-hemorrhagic hydrocephalus. These were pragmatic definitions based on majority consensus of the study neonatologists but lacked more robust grounds than this.

There was good adherence to the protocol and data completion was high for primary and secondary outcomes. Thirty-nine per cent of babies recruited to the PlaNeT-2/MATISSE study however had already received platelets prior to randomization. The study included important neonatal secondary outcomes such as sepsis, NEC, retinopathy of prematurity and bronchopulmonary dysplasia (BPD).[36] BPD, also known as chronic lung disease of prematurity, is defined as the requirement for supplemental oxygen or respiratory support at a corrected age of 36 weeks and PlaNeT-2/MATISSE is the only randomized study of platelet transfusions in the NICU that has reported bronchopulmonary dysplasia (BPD) as an outcome despite the clinical relevance of this in neonatology and biologic plausibility for causation. Even after adjustment for gestational age and initial severity of illness, BPD is among the

most significant predictors of future neuro-development impairment in infancy, early childhood and adolescence (57% vs 37% for VLBW matched infants) and 20% of babies with BPD have IQ scores < 70 compared to 11% of VLBW infants without BPD.[40] Survivors have high rates of asthma and diminished pulmonary function into adulthood. The PlaNeT-2/MATISSE study[22] demonstrated a higher rate of BPD in neonates in the higher transfusion threshold group. Platelets have significant immunologic and inflammatory effects which could mediate effects in the extensive pulmonary vascular bed.[41, 42] Preterm infants with BPD have higher levels of pro-inflammatory mediators on bronchoalveolar lavage compared to preterm infants who do not have BPD.[43] It is hypothesized that bioreactive components in platelet transfusions could contribute to the lung injury involved in BPD. In terms of neurodevelopmental follow up at two years of age the PlaNeT-2/MATISSE study is also strong in that is has achieved 92% follow up rates (awaiting analysis).

Secondary analysis of the trial results to assess heterogeneity of treatment effect by Fustolo-Gunnink et al[44] showed that smaller more preterm babies who were at highest baseline risk of major bleeding and mortality had a greater absolute risk reduction in association with the lower transfusion threshold. This important finding demonstrates that our clinical assumption that platelets may be of greatest benefit in this group (suggested by transfusion rates in ELBW infants[4]) is not true and prescribing prophylactic transfusions in this population may be proportionately more harmful. It is interesting to see the rapid acceptance of the new evidence presented by PlaNeT-2/MATISSE.[45]

There are risks associated with all blood product transfusions. Neonates have the longest potential lifespan living with adverse events associated with blood product transfusion. Despite massive advances in transfusion safety, donor exposure is still a risk. Transfusion of prophylactic platelets despite evidence for benefit appears to indicate that clinicians estimate these risks as low or may only be considering harm only in the form of transfusion associated blood borne infection, or TACO or TRALI. The PlaNet-2/MATTISE trial reported on general transfusion-associated adverse events although these were not clearly defined.[46] Neither Andrews[29] nor Kumar[33] reported on incidence of transfusion associated adverse events. Platelet transfusions have been independently associated with infection in critically ill patients either through direct (stored at room temperature) or indirect infection but sepsis rates were not reported in Andrews et al[29] although they were reported in the trial by Kumar et al[33] and the PlaNet-2/MATISSE trial[22]. Although the PlaNeT-2/MATISSE trial did not collect information on ABO incompatibility at the time of recruitment and platelet transfusion, the outcome demonstrating harm has triggered an additional study of platelet donor and storage characteristics in the PlaNeT-2/MATISSE cohort.

What additional research questions should we consider?

Which threshold should we chose for prophylactic platelet transfusion or should platelets only be administered to the bleeding baby?

One question to consider is which threshold should be used for non-bleeding preterm babies with thrombocytopenia? The PlaNet-2/MATISSE study[22] showed the lower threshold was less harmful but didn't establish a safe threshold for platelet transfusion. Should the neonatal community consider another threshold trial? Should it be limited to a more homogenous group of babies with either early or late thrombocytopenia? Is it ethical to redo the PlaNeT-2/MATISSE trial in another setting such as the United States? Adult trials have evaluated lower thresholds than those applied in the PlaNeT-2/MATISSE study but transfusion thresholds established in thrombocytopenic adults cannot be directly applied to neonates because of the major developmental differences in platelet function and hemostasis between preterm neonates and adults.[47] Future neonatal trials might consider transfusion thresholds similar to those studied in adults[48] or used in paediatrics.[49] There are potentially significant barriers to the success of such a trial: the neonatal community may not be ready for a threshold trial at those levels and it would be difficult to recruit an adequate sample size given the infrequency of platelets $<10x10^9$/L. Likelihood of protocol violation would also be a significant barrier to completion of a study of this nature.

What role does inflammation play in potential harm from platelet transfusions and how should we assess this in the neonatal population? It may be useful to consider what role Inflammation plays in potential harm from platelets. There is clear biologic plausibility for harm from platelet transfusion to neonates. Platelets are as important for host immunity, inflammation and angiogenesis as they are for haemostasis.[41] Although platelets lack a nucleus they contain messenger RNA and all the required transcriptional machinery required for protein synthesis. When platelets become activated they degranulate releasing a vast array of cytokines and chemokines, vasoactive agents, coagulation factors, adhesion molecules and growth factors that play a key role in modulating immune responses. Proinflammatory effects may enhance vascular permeability. IL-1, IL-6, TGB β, VEGF and TNFα appear to play a crucial role in the sequence of neonatal inflammation.[50] Platelet transfusions have been independently associated with infection in critically ill patients either through direct infection or through their effects on immunity.[42] Increased inflammation may explain the increase in mortality, bleeding and lung disease demonstrated in PlaNeT-2/MATISSE and lowering the dose used may reduce adverse effects of platelet transfusion. Assessment of bronchoalveolar lavage inflammatory markers in ventilated babies may have potential to identify the pulmonary inflammatory response to platelet transfusion. Fecal biomarkers of inflammation show promise in the diagnosis of NEC[51] – could they be potentially used to identify changes in inflammation?

What role does thrombosis play in platelet induced harm in this population?

There is also a potential role for studies assessing platelet transfusions and thrombosis. There are stark developmental differences between preterm recipient and adult donor. The neonatal hemostatic system is a finely balanced system where differences in platelet function are counterbalanced by a relative hypercoagulability of neonatal blood.[47] Neonates have shorter bleeding times despite hyporeactivity and decreased adhesive capacity of their platelets. We know that *in-vitro* neonatal platelets appear[50] to be hyporeactive relative to adult platelets, however we do not know if transfusing adult, more active platelets into the neonate causes a prothrombotic state that could promote microthrombosis. Determination of thrombosis in the neonatal population is difficult however and might precipitate a wave of unnecessary anticoagulation with all its attendant risks so studies in this area may not offer much clinical potential.[52]

What role does altered angiogenesis play in platelet induced injury, in particular retinopathy or prematurity?

We also need to understand the role of platelets in neonatal angiogenesis.[53, 54] Stimulation of α-granules in platelets and megakaryocytes can cause release of proangiogenic and antiangiogenic agents[55] which appear to be critical elements in the pathologic process of retinopathy of prematurity (ROP) which is a potentially devastating consequence of prematurity which can cause blindness. [56-58] Activated platelets may have a role in the pathogenesis of ROP.[58] Vascular endothelial growth factor (VEGF) is also associated with platelets,[59-61] and there have been multiple studies of ROP treatment using anti-VEGF monoclonal antibodies.[62, 63]

Does ABO incompatibility play a role in harm?

There is limited evidence regarding the ABO matching of platelets transfused to neonates. Although further analysis of the transfusions undertaken in the PlaNeT-2/MATISSE cohort, as is currently underway, may help elucidate this. The ABO blood group system is vital in transfusions that contain red blood cells, however its importance in platelet transfusions is not clear. Type O platelets and plasma have anti-A and anti-B antigens, which can cause the production of ABO immune complexes when non ABO-matched platelet transfusions are administered.[42] ABO incompatible platelets can be given for logistical reasons, with a study

on the pediatric critical care population demonstrating that 32% of the children in their study population receiving non-ABO matched platelets.[64] Unlike in the adult population, where any ABO incompatible platelets transfused can contribute to platelet refractoriness in adults, with a potential cumulative effect[42] and where ABO matched platelets can provide a greater platelet increment than ABO mismatched platelets[65], this study of the pediatric critical care population did not demonstrate any issues with the use of ABO mismatched platelet transfusions.[64] The evidence available in the neonatal population about ABO matched platelet transfusions is very limited, however in the adult population there is evidence of potentially deleterious effects of ABO-mismatched platelet transfusions.[66, 67]

Which volumes should be used in the setting of preterm prophylactic platelet transfusion?

The role of platelet transfusion volumes also needs to be considered. The volume of platelets administered could increase the role of inflammatory, thrombotic or angiogenic mechanisms. Production of systemic cytokines can disturb cerebrovascular autoregulation increasing likelihood of brain injury.[68-70] Large volume platelet transfusions may also potentially mediate harm through hemodynamic effects - from the rapid administration of a large volume of fluid into a pressure passive circulation[71] not just dose dependent platelet mediated inflammatory effects. Neonatal platelet transfusions are commonly administered at volumes (typically 15 mL/kg/transfusion) based on long-standing historical practice.[49]

There is little direct evidence for the neonatal platelet transfusion volumes of 10-20ml/kg in current use.[72] The standard platelet transfusion volume (15 ml/Kg, within the range 10-20 ml/kg) represents common neonatal practice going back several decades. The volume has been suggested by recent guidelines[49] and its use evidenced by surveys (Get it Right First Time (GIRFT) UK data 2020, personal communication from lead clinician). It is not based on the adult therapeutic dose of approximately 217mls (with $2.6x10^{11}$ platelets) which would mean that the average 70kg adult would get 3-4ml/kg in one transfusion. It may be based on previous beliefs that neonates need to maintain a higher platelet count than adults, and therefore require a more substantial platelet increment post-transfusion, which is reflected in prior transfusion practices in the neonatal population. Andrew et al in 1993 demonstrated an increment of $90x10^{9}$/L per 10ml/kg platelet transfusion,[29] and this has been used historically to support some guidance. The PlaNeT-2 study used 15ml/kg per platelet transfusion,[22] which was common practice in the UK between 2010 and 2018. This also corresponds with available guidelines internationally. Volume variation in the PlaNeT-2 trial was limited with a median of 15.2 ml/kg (IQR 14.8 – 16.3).[73] There is, however, no current robust evidence supporting this or any other neonatal platelet transfusion volume.

The PlaNeT-3 randomized controlled trial is due to start in 2021 and aims to demonstrate superiority, safety and efficacy of lower volume platelet transfusions in 370 thrombocytopenic preterm neonates less than 32 weeks' gestation and/or less than 1500g at birth. The trial will compare lower (5mL/kg) or standard volume (15mL/kg) transfusions in

babies with platelets <25x10^9/L. The primary outcome is death or major bleeding within 28 days of randomization. The trial will also assess blood levels of inflammatory mediators pre- and post-platelet transfusion, and record pre-defined transfusion associated adverse events.

How quickly should prophylactic platelet transfusions be administered?

The majority of neonatal transfusion treatment guidelines suggest platelets should be infused rapidly (30-60 minutes). This practice most likely derives from adult practice relating to acute major bleeding where limited intravenous access also necessitates rapid administration of product. This is not based on any published evidence and appears to be historical practice. This is likely due to concerns about the clumping and activation of platelets during transfusion, which may be unfounded. In fact, recent evidence suggests that platelets can safely tolerate up to eight hours off the agitator.[74] Substantial fluctuations in intravascular volume can be harmful to neonates, particularly a large volume bolus in a critically ill acidotic infant with a pressure passive cerebral circulation.[71] We need to reconsider guidance in this area based on research rather than precedent.

How can we predict which babies are most likely to be harmed by platelets?

Much research has been based around predicting which babies are most likely to bleed so that they can be prophylactically transfused. Our research emphasis may need to change as there is no evidence to suggest that extent of thrombocytopenia correlates with likelihood of bleeding or that prophylactic platelet transfusion is helpful in preventing bleeding or mortality. Recent evidence suggests that the converse is true. Should we consider which babies are at higher risk of adverse complications of platelet transfusions? This is likely to be the same cohort that neonatologists previously targeted for transfusion.[44] Given the potential for harm, should the alternate uses of platelet transfusions for indications other than bleeding - for example ROP[75] or PDA[33] - be discontinued?

There are limited data on TRALI and TACO in neonates, probably related to the difficulty in defining these conditions in this population. Better definitions are required for these conditions in the neonatal population in order to properly quantify potential transfusion-associated harm.

Summary

There is no evidence that prophylactic administration of platelet transfusions to non-bleeding preterm neonates with severe thrombocytopenia reduces bleeding. Despite this, neonatologists frequently prescribe these transfusions. We are using volumes and rates of transfusion based on historic precedent and we only poorly understand the etiology of harm from platelet transfusions. We have much to learn about this commonly used therapy in neonates. The good news is that there are enough potential studies in this critically important and relevant research area to generate research for decades.

Declaration of Interest

None.

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