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Safety and feasibility of platelet transfusion through long catheters in the neonatal intensive care unit: an in vitro study

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ABSTRACT

Objective To assess the safety and feasibility of platelet transfusion through small-bore long lines used in the neonatal intensive care unit (NICU), including double-lumen umbilical venous catheters (UVCs) and 24 G and 28 G peripherally inserted central catheters (PICCs).

Design Prospective in vitro controlled study.

Setting Blood transfusion service laboratory.

Methods In vitro platelet transfusions were set up as per NICU practice. Transfusion line pressure was monitored. Post-transfusion swirling, presence of aggregates, pH analysis and automated cell count in vitro activation response by flow cytometry assessing CD62P expression were assessed.

Main outcome measures All transfusions completed successfully. The rate of infusion was reduced in 5 of 16 transfusions through 28 G lines due to 'pressure high' alarms. There was no difference in swirling values or transfusion aggregate formation, CD62P expression levels, platelet count, platelet distribution width, mean platelet volume, plateletcrit or platelet to large cell ratio across transfusions post-transfusion.

Conclusions This study showed that in vitro platelet transfusion performed through 24 G and 28 G neonatal PICC lines and double-lumen UVCs is non-inferior to 24 G short cannulas, using outcome measures of platelet clumping, platelet activation and line occlusion. This suggests that where available these lines can be used if necessary for platelet transfusion.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is very limited evidence available on transfusing platelets through long lines that are used in the neonatal intensive care unit (NICU), including umbilical venous catheters and peripherally inserted central catheters.
⇒ There are anecdotal concerns that platelet transfusions could block long lines used in the NICU.

WHAT THIS STUDY ADDS

⇒ In vitro platelet transfusion through long lines used in the NICU is feasible and safe.
⇒ There is no difference in platelet count, size or levels of activation post-transfusion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that when long lines are available in the NICU they may be safe to use for platelet transfusion.

INTRODUCTION

Platelet transfusions are a common intervention in critically ill premature infants often performed in the setting of thrombocytopaenia related to sepsis or necrotising enterocolitis. Platelet transfusions are usually administered through a peripheral intravenous line. These lines are used, even in the setting of poor venous access and an available central line, due to clinical concerns about potential clotting and blockage of the central line.

In the neonatal intensive care unit (NICU), commonly used lines for central venous access include umbilical venous catheters (UVC), inserted into the umbilical vein, and peripherally inserted central catheters (PICCs), inserted through a peripheral vein into the central circulation. Due to the small size of neonatal vasculature, especially in extremely low birthweight infants, with a birth weight less than 1000 g, very small-bore PICCs of 24 G and 28 G (internal diameter 0.311 mm and 0.184 mm) are used. UVCs can be single, double or triple lumen and can be with much larger bore than a PICC, with up to an internal diameter of 1.5 mm, or more commonly an internal diameter of 0.603 mm. Anecdotal concerns deterring clinicians from transfusing platelets through central lines include platelets potentially clumping in the line and causing obstruction, and/or platelet activation. Evidence suggests that platelet activation could occur due to shear stresses,[1 2] and due to the relatively long length and small bore of long lines in the NICU shear stresses are likely to be high. When activated, platelets release inflammatory mediators, stimulate thrombus formation and promote inflammation.[3 4]

Individual neonatal unit guidelines may specify which lines to use but there is no national neonatal or blood transfusion service guideline in the UK or Ireland on the use of central lines in common use in the NICU. Although some studies have investigated red cell transfusion through larger PICC lines,[5] few studies have analysed the feasibility and safety of transfusing red cells through extra-small (27 G) and small (24 G) PICCs and no published studies have assessed platelet transfusion through any of these lines.[6–8] In this study we used an in vitro model to mimic preterm infant transfusion to

assess the feasibility of performing platelet transfusions through commonly used neonatal central lines.

Aim

The aim of this study was to demonstrate the feasibility and safety of transfusing platelets through central lines, including UVCs and 24 G and 28 G PICCs, through measurement of potential catheter blockage, inline pressure levels and platelet activation in an in vitro model. The secondary objectives included assessment of platelet clumping by assessment of aggregates in the platelet transfusate, differences in swirling, platelet count and mean platelet volume (MPV).

METHODS

We performed a non-inferiority in vitro study comparing neonatal PICC lines and UVCs with the standard peripheral 24 G short catheter.

Study population

Regular male apheresis donors (blood group O+, cytomegalovirus (CMV) antibody-positive) were consented to participate in this study (N=16). All platelet donations were collected and analysed at the National Blood Centre of the Irish Blood Transfusion Service. Eligible donors were informed of the study and invited to participate 28 days prior to platelet donation. Consent was confirmed on the day of donation. Double platelet donations were collected by apheresis using Trima Accel (Terumo, Tokyo, Japan). Platelets were processed as routine for neonatal-suitable transfusions, including the assessment of pre-release blood cell count (Sysmex XN Series, Sysmex Europe SE, Norderstedt, Germany) and bacterial culture (BacT/ALERT, BioMerieux, Bruz, France). Neonatal platelets are released for transfusion usually on day 2 postdonation.

Platelets were gamma-irradiated, and irradiation was confirmed with RadTag (Sarstedt, Nümbrecht, Germany).

Platelet transfusion set-up

The following polyurethane catheters were used: Premicath 1 Fr/28 G 20 cm (Vygon, Ecouen, France), polyurethane catheter Nutriline 2 Fr/24 G 30 cm (Vygon), polyurethane double-lumen umbilical catheter 4 Fr, 2 20 G lumen (Vygon) and the peripheral 24 G short-catheter Jelco Optiva (ICU Medical, California, USA) as a control. Platelets were also run through 'no line', straight into the collection set, to simulate the same handling.

Platelets (60 mL) were drawn from the platelet bag into a 60 mL BD Plastipak (Becton Dickinson, Madrid, Spain) syringe through a B Braun ProSet Sangofix B-Set 200 μm, 11 cm^2 filter (B Braun, Melsungen, Germany). The syringes were connected to the infusion lines through a CareFusion PA-80-GC extension set (Sendal, Almaraz, Spain) with a Bionector needle-free access device (Vygon). Platelets were infused through a B Braun Perfusor Space pump (B Braun), with pressure alarms set at maximum (900 mm Hg), as per normal neonatal unit practice for PICC line infusions. Platelets were infused into labelled Compoflex DEHP/PVC 150 mL bags (Fresenius Kabi, Hamburg, Germany) in a 37°C water bath based on neonatal body temperature (figure 1).

Infusions were run at 30 mL/hour for 2 hours, mimicking a 15 mL/kg transfusion in a 1000 g baby which would normally be administered over 30 min at the fastest rate of transfusion. To have sufficient transfusate to perform all the testing planned, 60 mL was transfused.

During the transfusions, transfusion-line pressure was monitored by the investigator using the visual scale on the Perfusor Space pump, and the highest pressure level attained was recorded for every transfusion. Following the 2-hour transfusion period, the Compoflex bags were removed from the water bath and dried, the transfusion lines were removed, and the Compoflex bags were heat-sealed using the SEBRA Hand-Held RF Tube Sealing System (Vante Biopharm, Arizona, USA).

Figure 1 Set-up of laboratory transfusions using syringe pumps, lines and water bath.

Bags were assessed for the level of swirling and the presence of aggregates by a senior medical scientist or a transfusion scientist. Visual swirling assessment was scored from 0 (no swirling) to 3 (optimal swirling) as per Bertolini and Murphy.[9] A visual aggregate assessment score was assigned as recommended by van der Meer *et al*.[10] Aliquots of transfused platelet concentrates were then removed from the bag for pH analysis (Roche Omni S, Roche Diagnostics, West Sussex, UK) and automated cell count (Sysmex XN Series, Sysmex Europe SE). Aliquots were also removed for platelet in vitro activation response, estimated by flow cytometry (FACSCanto II Benchtop Flow Cytometer System, BD Biosciences, New Jersey, USA), assessing the expression of CD62P following staining with fluorescein isothiocyanate (FITC)-conjugated anti-CD62P antibody (BD Biosciences).

Statistical analysis was completed using SPSS Version 27. The primary outcome was successful transfusion of platelets. Secondary outcomes included maximum pressure reached on infusion pump during transfusion, presence and degree of swirling in the transfusate, presence of aggregates in the transfusate, platelet count and MPV, and pH and CD62P levels as a marker of platelet activation. As data were not normally distributed, the independent-samples Kruskal-Wallis test was used to determine if there were any significant differences in the post-transfusion parameters between groups.

RESULTS

Donations

Sixteen platelet donors donated 32 adult treatment dose units of platelets. All donors were blood group O+. All donors were male, aged between 20 and 61 years old, with a median age of 52 years. Donor body mass index ranged from 25.5 kg/m^2 to 35.5 kg/m^2, with a median of 29.5 kg/m^2. Donations were collected on Mondays and Tuesdays over 5 weeks in April, May and June 2022.

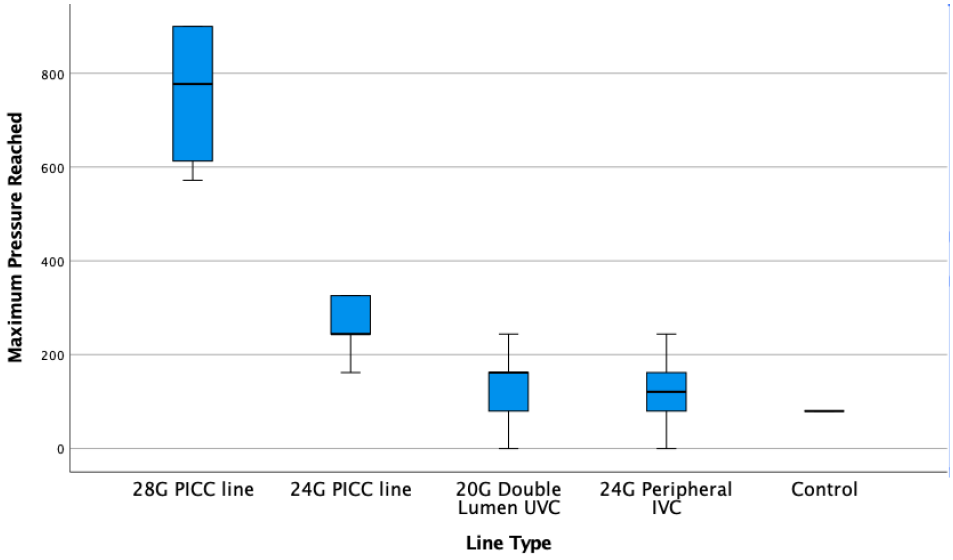

Figure 2 Boxplot of maximum pressures in mm Hg reached during simulated transfusion across all groups. PICC, peripherally inserted central catheter; UVC, umbilical venous catheter; IVC, intravenous catheter.

Transfusion parameters

All 80 transfusions completed successfully. Of the 16 transfusions through the 28 G PICC line, 5 had to have their rate of infusion reduced by 1 mL (3.3%) per hour due to 'pressure high' (>900 mm Hg) alarms.

The maximum pressures recorded in the groups are outlined in figure 2. The highest pressures were reached at a median of 8 min (range 7–19 min) into the transfusion.

Platelet parameters

There was no difference in pretransfusion and post-transfusion swirling values or aggregate formation across transfusions. However, all transfusions from a single donor (through all lines and control) developed aggregates and therefore this was considered a donor-related event, unrelated to the transfusion lines.

We did not find differences across or between groups in the post-transfusion level of expression of CD62P (figure 3). Similarly, there was no difference across or between groups in post-transfusion platelet count, platelet distribution width, MPV, plateletcrit or platelet to large cell ratio.

DISCUSSION

Neonatal platelet transfusion has largely been based on historical practice, although recent evidence suggesting harm from prophylactic platelet transfusion at lower thresholds has prompted re-evaluation of how we use this blood product.[11–13] This is the first study to formally assess platelet transfusion in lines in use in NICU and demonstrates that platelet transfusion is feasible through central lines of varying sizes without significant signs of platelet activation or aggregation.

Critically unwell babies in the NICU may not be feeding enterally and therefore depend entirely on their venous access for all medications, including inotropes, fluids and parenteral nutrition. Notwithstanding the potential theoretical disadvantages of clotting and activation, there are several advantages to using available central lines to administer platelet transfusions. Although central venous access comes with a risk of sepsis,[14 15] it can avoid repeated skin breakages in the attempt to secure a peripheral intravenous cannula. Repeated attempts to secure peripheral intravenous cannula access are also painful.[16] The skin of preterm neonates is especially fragile and vulnerable to infection.

This study demonstrates that platelet transfusion is feasible through the smallest lines that we use in the NICU, showing that if peripheral venous access cannot be obtained central lines can be used. Infusion through these lines does not appear to compromise the platelets in the transfusion. Some babies who receive platelet transfusions can be critically unwell; for example, a baby who is undergoing therapeutic hypothermia can have significant peripheral vasoconstriction, making intravenous access difficult. As most UVCs are at least double lumen, we feel that this study supports the use of these catheters for platelet transfusion. Central access may not be appropriate for transfusion, however, in a setting of a single-lumen PICC line and continuous inotrope

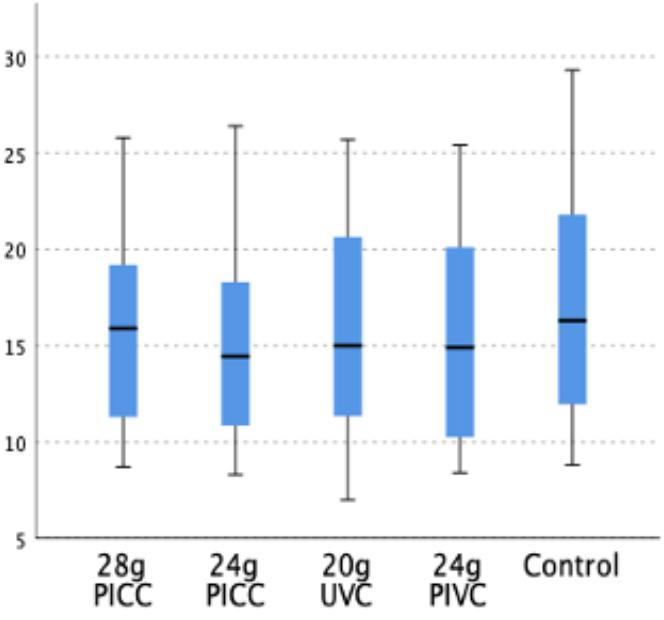

Figure 3 Boxplot of CD62P expression levels (as a marker of platelet activation) across all groups. PICC, peripherally inserted central catheter; UVC, umbilical venous catheter; PIVC, peripheral intravenous catheter.

infusions. We also acknowledge that 'breaking' a line also comes with higher risks of sepsis.[17] What this study can offer, however, is increased flexibility in terms of platelet administration. It is likely that neonatal central lines can be used for platelet transfusion without compromising the line or aggravating platelet activation and potential inflammatory sequelae. An additional finding in our study was substantial donor-level variation in the level of CD62P expression across the different donations. Although this is not a novel finding, it reminds us that donor platelets are a highly variable unpredictable product that we only poorly understand.

This study has several limitations. It is an in vitro not an in vivo study. We did not physically assess the lines post-transfusion and so we could not assess their structure post-transfusion. How a venous access line is fixed (particularly if the line is coiled) could further reduce the cross-sectional area, as NICU PICC lines are often coiled to fix them.[18–20] We did not assess this. We also did not assess the effect of multiple transfusions due to the collection method and water bath. In vivo transfusions are usually 30–60 min long, compared with the longer transfusion used in our study to collect minimum volumes to reassess swirling and aggregates. In vivo there is also a constant flow of blood along the tip of the line, which means that the platelets are in the circulation immediately. This could impact the activation of the platelets compared with the 2-hour infusion time that was used in the study.

In vivo studies could be considered; however, a clinical study in babies in NICU assessing platelet increments, activation or function would require extra phlebotomy in an already vulnerable group, and studies of clinical bleeding would require very large numbers of babies to pick up a signal. A follow-up in vitro study of platelet transfusions through 28 G catheters at different infusion rates with closer assessment of pressure could be considered.

CONCLUSION

This study showed that in vitro platelet transfusion performed through 24 G and 28 G neonatal PICC lines and double-lumen UVCs is non-inferior to 24 G short cannulas, using outcome measures of platelet clumping, platelet activation and line occlusion. This adds to the evidence base around neonatal platelet transfusion.

Contributors CMM designed the study, wrote the study protocol, performed all study transfusions and wrote the first draft and the last version. CMM is the guarantor. All authors were involved in the study set-up and logistics. SB recruited donors and obtained consent. AL and LM performed the flow cytometry. HC supervised all laboratory work. AF and AW supervised the research activity in NBC. All authors revised the first draft of the manuscript and approved the final version.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the National Maternity Hospital Research Ethics Committee (EC 12/2022). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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