strategy with an exciting future. This contribution by Su et al is a crucial step forward in the development of miRNA therapies targeting myeloid diseases and provides a foundation to build upon to further refine and innovate miRNA conjugate therapeutic strategies for other cell types. This conjugate method offers several advantages, including limited or no cytotoxicity in nonmyeloid cell types, myeloid targeting, and miRNA-mediated immunomodulation. As such, this is an attractive approach for other prospective miRNA or anti-miRNA therapeutics or as a mechanistic tool for dissection of miRNA function in myeloid biology.

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Comment on Jaffray et al, page 220

Diversifying study design in pediatrics

Fiona Newall | Royal Children's Hospital

In this issue of *Blood*, Jaffray et al report the increased association of percutaneously inserted central catheters (PICCs) with both catheter-associated venous thromboembolism (VTE) and catheter-related blood stream infection compared with tunneled central venous access devices.[1]

Their study is important for 2 reasons. First, the multicenter, prospective, observational cohort study design used by Jaffray et al enabled them to complete a pediatrics study with 1742 unique participants. As detailed in the 2006 commentary by Massicotte et al,[2] performing successful clinical trials with pediatric patients is fraught with challenges unique to this type of cohort. The recently published study by Male et al[3] that reported on the phase 3 trial of rivaroxaban vs standard of care in children with acute venous thrombosis demonstrates that these trials can in fact be completed successfully, but they remain challenging for several reasons. One of the main reasons is that thrombosis in children is increasingly recognized as a rare disease, with significant heterogeneity existing within study cohorts, as is evident in the Jaffray et al study. It is challenging to conduct a randomized trial that is able to recruit sufficient numbers of patients to mitigate this heterogeneity, even with the support of pharmaceutical sponsors. In publishing this study, Jaffray et al demonstrate that novel trial designs can successfully generate robust data with the power to inform clinical practice.

The second point, inextricably linked to the first, is that the number of participants recruited to the Jaffray et al study enabled the application of robust statistical analysis that generated findings with relatively tight confidence intervals for a study investigating thrombosis in children. There is evidence of disproportionate representation across the 2 groups in this study; children with PICC lines in situ contributed 64% of the total study population. In addition, there are differences in characteristics between the 2 groups: children with a PICC in situ tend to be older and less likely to have cancer compared with children with tunneled lines in situ. Nonetheless, the number of participants recruited across the 4 tertiary centers enabled the authors to perform meaningful analyses beginning with univariable analyses followed by a multivariable analysis.

There are some important points to note in the Jaffray study. First, the authors justify their use of Doppler ultrasonography to diagnose 94% of VTEs on the basis of the 2018 American Society of Hematology guidelines for the diagnosis of VTE.[4] The data informing that guideline is essentially derived from adult participants; studies that specifically focus on upper-limb VTE, as seen in the Jaffray study, have much smaller numbers of patients compared with studies that validate Doppler ultrasound for diagnosing lower-limb VTE. This evidence is at odds with the 2002 study by Male et al,[5] which demonstrated significant limitations in the sensitivity of Doppler ultrasound in diagnosing upper-limb VTE in children, with the exception of the jugular vessels. As with many clinical scenarios, the extrapolation of evidence generated from studies in adults needs to be applied very cautiously to pediatric populations because there are significant differences in hemostasis, thrombosis etiology, and anticoagulant response in children compared with adults. Second, Jaffray et al excluded infants younger than 6 months of age from participating in this study. Although their rationale for this exclusion is justified, it does preclude application of these findings to a cohort of pediatric patients who are significant contributors to the workload of pediatric

hematology departments. Finally, the significantly higher risk of catheter-associated blood stream infection identified in children with PICC lines compared with tunneled central lines represents a significant call to arms for international tertiary pediatric centers. Does the hazard ratio of 1.6 (95% confidence interval, 1.2-2.2) reflect a lapse in aseptic technique in the insertion and/or management of PICCs compared with tunneled central venous access devices? As postulated by Jaffray et al, could this inflated risk be attributable to the predominant antecubital fossa insertion location of the PICC? Given the significant association between infection and thrombosis, this association cannot simply be relegated to the domain of infection prevention and control departments but needs to be duly considered by those clinicians with subspecialty focus within pediatric hematology.

The study by Jaffray et al is timely, given the increasing complexity of infants and children being seen in international tertiary health services, very likely contributing to the widely reported increasing incidence of VTE.[6] As the authors concluded, decision-making processes used by clinicians in choosing placement for vascular devices is imperative to minimizing the risk conferred to some of our most vulnerable patients. Research designs such as that used by Jaffray et al could readily be adapted to evaluate clinical outcomes achieved by multicenter collaborations aimed at reducing variation in care related to the selection and insertion of central venous access devices in children. Such studies could generate data similarly powered to provide strategic guidance to clinicians in the prevention of catheter-associated infection and thrombosis in children.

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