Research Protocol

Project Details

Investigators
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Scientific Title
Cyanoacrylate glue for reducing bleeding after peripherally inserted central catheter insertion in neonates: a randomised controlled trial.

Lay Description
Babies in intensive care nurseries often have long-term lines inserted into their veins. The insertion site can continue ooze blood and affect the integrity of the dressing. We are studying whether using medical glue when the line is inserted can reduce the rate of bleeding afterwards. Glue may also be able to reduce the rate of lines accidentally coming out, as well as helping prevent babies from developing line-related infections.

Research Site
Neonatal Critical Care Unit
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Background

Literature Review
Peripherally inserted central catheters (PICCs) have become a routine aspect of care in neonatal intensive care units (NICUs) worldwide[1]. Being simpler to insert than central venous catheters (CVCs), PICCs provide essential long-term vascular access for nutrition, fluids and medications in premature and unwell neonates. Line-related complications and associated interruption of therapy can have significant ramifications for a neonate's health, as well as health service implications in terms of cost and additional workload. A variety of complications have been linked to unintended early PICC removal including catheter occlusion, rupture, extravasation, loss of dressing integrity, dislodgment and catheter-associated bloodstream infection (CLABSI)[2-3]. Early neonatal PICC removal due to these factors is relatively common, with recent studies describing rates of between 37.2%[2] and 39.3%[3]. An important consideration in this regard is the method of line securement used. Neonatal PICCs are typically secured with combinations of adherent dressings and sutureless securement devices depending on the particular unit's practices[1].

Effective securement is essential to avoid complications such as lost dressing integrity, line dislodgment and CLABSI from skin organisms.

A recent development in vascular access device (VAD) securement has been the use of medical-grade cyanoacrylate glue. Cyanoacrylate has been widely used for many years as an instant adhesive for both industrial and household purposes. Its use as a tissue adhesive began in the 1970s with the first-generation formulation of n-butyl-cyanoacrylate (BCA), which had the limitations of brittleness and possible skin irritation[4]. Subsequent development of the second-generation formulation of 2-octyl-cyanoacrylate (OCA) led to formal approval for medical use by the United States Food and Drug Administration (FDA) in 1998 as the product "Dermabond". OCA has higher tensile strength, more flexibility and reduced thermal reaction compared to BCA[4]. Cyanoacrylate as BCA, OCA and combination formulations has subsequently been used extensively for wound closure and various surgical applications. Tissue adhesive use for VAD securement is a more recent development, which initially relied on off-label use of existing products with excessive volumes and wastage[5]. The first tissue adhesive for VAD securement was FDA approved in 2017 as the combined BCA/OCA product "SecurePortIV", addressing these limitations with a purpose-built design containing a small volume of adhesive. Importantly when considering the safety of adhesive use for VAD securement, cyanoacrylate has been demonstrated in vitro to have no weakening effect on a variety of both polyurethane and silicone catheters[6-7].

Research on the benefits of tissue adhesive for VAD securement has been growing in the past decade, with a particular focus on improvement of post-insertion bleeding, prevention of line dislodgment and reduction in line-associated infection. With respect to achieving early haemostasis, cyanoacrylate glue has also been shown to have favourable effects after VAD insertion. In vitro research has demonstrated that cyanoacrylate exerts a potent haemostatic effect, with an activated clotting time twelve times faster than thromboplastin[8]. Tissue adhesive has been shown to eliminate bleeding after insertion of PICCs and CVCs in adult patients[9-10], which is often problematic and can lead to loss of dressing integrity and early dressing changes. In a study of paediatric patients, cyanoacrylate similarly reduced early bleeding after PICC insertion and was shown to prolong the time until the first required dressing change[11].

Cyanoacrylate has also demonstrated favourable properties with respect to the strength of VAD securement and prevention of line dislodgment. In vitro studies have demonstrated that tissue adhesive demonstrates equal or superior securement strength to more widely used conventional dressings[7,12]. This has translated to improved clinical outcomes, with a recent randomised controlled trial in adult patients demonstrating significantly less dislodgment of peripheral intravenous cannulae with use of cyanoacrylate glue compared to traditional securement techniques[13]. Additionally, a recent retrospective cohort study explored the effect of cyanoacrylate adhesive specifically on neonatal PICCs and reported a reduction in dislodgment rate from 14% to 1%[14].

With respect to preventing line-related infection, lab studies have demonstrated that cyanoacrylate inhibits the growth of Gram-positive organisms[7,15]. Cyanoacrylate has also been shown to create an impermeable barrier to microbial penetration, while traditional dressings allow bacterial penetration in up to 99.3% of cases[16]. A more recent study has also shown that in addition to activity against Gram-positive organisms, OCA formulations also have antibacterial properties towards Gram-negative organisms[17]. Despite these favourable antimicrobial properties, no research has yet been performed to directly investigate the effect of cyanoacrylate on CLABSI rates. CVAD bundles including tissue adhesive among other interventions have been found to reduce infection rates in both children[18] and neonates[19]. Additionally, a recent study

found that cyanoacrylate is as effective as chlorhexidine soaked sponges in eliminating microbial colonisation at the exit site of PICC lines[20].

Research Rationale

The vast majority of research on cyanoacrylate glue for VAD securement has been performed in adult and paediatric patients. A handful of papers have described the use of cyanoacrylate in neonates for CVC[21-22] and PICC[14] securement. None of this literature reported any adverse outcomes from tissue adhesive across a wide array of neonates including extremely premature gestations. Only one research study has been published in neonatal patients by D'Andrea et al[14], using a retrospective cohort design that found a reduction in PICC dislodgment rate using cyanoacrylate glue from 14% to 1%. Our research proposal addresses this paucity of evidence for the use of cyanoacrylate in neonatal VADs, with a particular focus on neonatal PICCs given their widespread use in NICUs worldwide. As summarised above, cyanoacrylate has demonstrated promising haemostatic, securement and antimicrobial properties in lab research. These properties have translated in clinical research to reductions in post-insertion bleeding and line dislodgment, as well as theoretical but as yet unproven benefits for the reduction of CLABSI.

A recent audit of PICC lines in our NICU demonstrated a very high rate of post-insertion bleeding of 81% across 30 catheters. By comparison, dislodgment is a rare event in our unit with none of the audited lines losing securement. CLABSI also did not occur in any of the audited lines and the current surveillance rate in the unit is only approximately 8 infections per 1000 line days. Given the implications of these differing incidence rates for achieving adequate statistical power, our study will focus on the effect of cyanoacrylate glue on post-insertion bleeding. A subsequent study could investigate the effect of cyanoacrylate on CLABSI rates, with a much larger sample size to ensure adequate statistical power. This would be a particularly compelling and novel study, as the promising antimicrobial effects of cyanoacrylate have yet to be directly explored in clinical research.

Aims & Objectives

-*Aim* — The study aim is to evaluate the benefits of cyanoacrylate glue when used for the securement of neonatal PICC lines.
-*Primary Objective* — Our main objective is to determine whether cyanoacrylate glue reduces the incidence of post-insertion bleeding when used for securement of neonatal PICC lines.
-*Secondary Objectives* — Our secondary goals are to confirm the safety and utility of cyanoacrylate glue in neonates, as well as determining whether its use affects the observed rate of line dislodgement or CLABSI. This may inform the rationale and design of future studies primarily addressing these outcomes.

Methodology

Design

Randomised controlled trial. Two-arm study of superiority.

Population

-*Inclusion Criteria* — Any neonates requiring PICC line insertion will be considered.
-*Exclusion Criteria* — Neonates with a history of adverse skin reactions with dressings/adhesives would be excluded, as well as in those whose parent/s are unable to give informed consent.
-*Sample Size/Power* — We have sought statistical advice for our sample size calculation from Alison Griffin, a biostatistician in the Statistics Unit at the QIMR Berghofer Medical Research

Institute. For this calculation, we have revised our baseline incidence of post-insertion bleeding from 81% detected in our small audit down to 70% to better reflect the actual rate that this may occur. We have used a reduction of 30% incidence for our power calculation as this would be considered clinically significant – from 70% to 40%. This resulted in a baseline sample size of 84 neonates. We have allowed for approximately 10% loss to follow-up, while noting that there is likely to be minimal loss to follow-up given the nature of the study with neonates always remaining admitted to the unit for the duration of having a PICC line in situ. This resulted in a final sample size of 92 babies split into 46 per group. For our calculation, we have used the statistical parameters of α=0.05 (probability of type I error) and β=0.2 (probability of type II error).
-*Duration* — Anticipated to be 6 months based on typical numbers of PICC lines in our unit.

Outcomes
-*Primary* — Our primary outcome is post-insertion bleeding at 24 hours after PICC line insertion. This is a dichotomous outcome (present/absent).
-*Secondary* — Our secondary outcomes are the incidence of line dislodgment, CLABSI and adverse skin reactions related to the use of cyanoacrylate. These are all also dichotomous outcomes (present/absent).

Device Information
-*TGA ARTG Identifier* — 314713
-*Trade Name* — SecurePortIV
-*Generic Name* — Cyanoacrylate (combination BCA/OCA)
-*Manufacturer* — Adhezion Biomedical LLC
-*Approved Indication* — Intravenous catheter holder
-*Manufacturer Instructions* — To be applied as a film forming securement and sealant at the point of vascular access catheter skin entry. The film holds the catheter to the skin to reduce catheter movement, migration, and/or dislodgment. It is used to protect the catheter skin entry site by creating a sealant that immobilizes surface bacteria, preventing them from entering into the catheter skin entry site while also providing a moisture barrier. Intended to be used with a transparent film dressing on short-term and long-term vascular access catheters including peripheral IVs, PICCs and CVCs.

Procedures
-*Recruitment* — When a decision has been made to insert a PICC line into a neonate, the medical officer (MO) or neonatal nurse practitioner (NNP) will confirm the absence of exclusion criteria and start recruitment of the baby into the study.
-*Consent* — The MO/NNP will seek written consent for the study as an addition to the existing consent process for PICC insertion. The study has associated Consent Forms and Participant Information Sheets which will be given to all parents of neonates involved in the study. Language and cultural support services will be used if required to ensure adequately informed consent is obtained. This would involve translation of our consent and information sheets by a medical interpreter and use of an interpreter for consent discussions.
-*Randomisation* — Mater Research will generate a simple randomisation schedule for our study with participant identification numbers for each baby and an allocation to either the treatment or control group. This randomisation schedule will be provided to a research assistant not directly involved with the study, as well as detailed instructions on how to generate labels, cards and envelopes. Each envelope will be labeled with a participant number (eg A001) and contain two cards — an allocation card (control/treatment) and a data collection card. The envelopes will be opaque to prevent unblinding and sealed. The envelopes will be made available within the unit for MOs/NNPs who are inserting lines.

After obtaining consent, the MO/NNP would open an envelope to determine which group the neonate would be allocated to. The allocation card would be placed back into the envelope and re-sealed and kept in the neonate's chart. The data collection card would be left in the baby's chart for subsequent use. All envelopes and cards would have to be accounted for at the end of the study.

-*Control Arm* — Routine PICC line insertion (sterile technique, chlorhexidine skin preparation, insertion of 24G/28G PICC via introducer needle/cannula, confirmation of correct placement with contrast-enhanced x-ray), standard adhesive dressings applied (Steristrips and Tegaderm).

-*Intervention Arm* — Routine PICC line insertion as per the control arm, 0.15mL of cyanoacrylate glue applied to the insertion point via SecurePortIV applicator device, standard adhesive dressings applied as per the control arm.

-*Data Management* — Microsoft Excel will be used for data collection and storage. The two spreadsheets into which data is entered will be password-protected, kept on secure Mater network storage and accessible only to the two investigators. Data will be retained for 15 years from the date each neonate reaches 18 years of age.

-*Data Collection* — The day following PICC insertion, the neonate's bedside nurse would record information using the data collection card left in the baby's chart. This card would include the following fields — participant number, UR number, post-insertion bleeding and skin reaction. The nurse would inspect the insertion site for evidence of skin reaction and any blood seen underneath the dressings would be recorded as positive post-insertion bleeding. It should be noted that cyanoacrylate is transparent and would not be able to be seen underneath the dressings, so observation of the insertion site would not reveal the neonate's allocation. The nurses collecting data would thus remain blinded to treatment allocation. Data collection cards would then be placed in a secure location in the unit to be collected by the study investigators. Data would be recorded in two secure spreadsheets by the study investigators. The first spreadsheet would be a list of participant numbers matched to UR numbers. The second spreadsheet would include the participant number and all other parameters. This would ensure de-identification of the data used for analysis, as well as maintaining a log linking participant numbers and UR numbers should this be required. The study investigators would digitally access the baby's scanned notes to complete the other data parameters — gestation, birth weight, diagnoses, PICC type, insertion site, line dislodgment or CLABSI.

-*Data Analysis* — We have sought statistical advice for our outcomes analysis from Alison Griffin, a biostatistician in the Statistics Unit at the QIMR Berghofer Medical Research Institute. Incidence rates for our study's primary and secondary outcomes will be determined for each study arm. For our primary outcome of post-insertion bleeding, any difference between the two arms will be evaluated by calculation of 95% confidence intervals and p-values. $p < 0.05$ will be considered statistically significant. For each of our secondary outcomes, we will report absolute risk reduction and/or relative risk reduction with 95% confidence intervals.

-*Blinding* — Blinding at time of intervention is not possible due to the nature of cyanoacrylate. As such the clinician inserting the line would be aware of the neonate's allocation, but would be instructed to keep this confidential. Outcome assessors will be blinded to allocation as cyanoacrylate glue is not visible under dressings after application. The statistician will also be blinded to allocation, as spreadsheet data will not provide any indication of which group a baby is assigned to. The only way to determine the neonate's allocation would be linking their participant number to their allocation using the randomisation schedule generated by Mater Research. The schedule will not be accessible to anyone involved in the study aside from the initial research assistant, who will generate envelopes and cards.

-*Patient Safety* — Any adverse skin events relating to use of cyanoacrylate glue will be recorded and reported per Mater Health institutional requirements and followed-up by the research team. Management of these events would involve removal of the overlying dressings and the glue itself,

which is easily removed from the skin using adhesive removal wipes. The affected skin area would then be monitored as per existing unit policies and procedures surrounding skin integrity assessment. Unexpected serious adverse events would follow a similar institutional process, as well as further reporting to the Human Research Ethics Committee and Therapeutic Goods Administration.

Ethical Implications

Our research will be conducted in full conformance with the principles of the NHMRC National Statement on Ethical Conduct in Human Research. The primary ethical consideration in our study relates to the relatively novel use of cyanoacrylate glue for neonatal VAD securement and the potential for adverse skin reactions. While tissue adhesive has been shown to be well tolerated in adult and paediatric patients, neonates have particularly fragile skin especially at earlier gestations. Fortunately, recent literature has confirmed the safety of cyanoacrylate in a broad range of neonates. D'Andrea et al[14] used cyanoacrylate glue for PICC securement in 172 neonates with birth weights between 480-3270g and reported no adverse effects. Barone et al[22] used cyanoacrylate for CVC securement in 30 neonates with birth weights between 370-1240g and gestations between 23-32 weeks, similarly without any adverse effects reported. Ostroff et al[21] also reported no complications from the use of the specific cyanoacrylate product planned for our study (SecurePortIV), when used for CVC securement in 82 neonates with birth weights 450-3345g and gestations 23-39 weeks.

Results & Outcomes

Dissemination

Publication of our study will be undertaken in a relevant healthcare journal. Our results will also be disseminated locally within our unit, as well as being presented at relevant local, national and international meetings. Based on the results of the study, this may lead to practice change within PICC insertion guidelines. Additionally, part of our consent process will include offering parents the option of providing their contact details to send them the final results of the study.

Further Research

As discussed earlier, our trial may lead to a larger study with sufficient statistical power to explore the effect of cyanoacrylate glue on CLABSI rates. While tissue adhesive has been shown to have favourable antimicrobial properties in lab studies, this has yet to be direct explored in clinical research. CLABSI incidence is an important issue in neonates, given their greater vulnerability to infection compared to adults and children. Should the antimicrobial properties of cyanoacrylate help protect neonates from CLABSI, this could lead to significant practice change and would represent a compelling and novel finding.

Glossary of Abbreviations

BCA — n-butyl-cyanoacrylate
CVC — central venous catheter
CLABSI — catheter-associated bloodstream infection
FDA — United States Food and Drug Administration
MO — medical officer
NHMRC — National Health and Medical Research Council
NNP — neonatal nurse practitioner
NICU — neonatal intensive care unit
PICC — peripherally inserted central catheter
VAD — vascular access device

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