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RESEARCH PROTOCOL

Peripherally Inserted Central Catheter OutcoMes PolyurethAne veRsus Endexo: the PICCOMPARE Trial. Protocol for a randomised controlled trial

Author(s): Tricia Kleidon RN, MN*
Lady Cilento Children's Hospital, Brisbane, Qld, Australia
Alliance for Vascular Access Teaching and Research (AVATAR), Menzies Health Institute Queensland, Griffith University, Brisbane, Qld, Australia

Amanda Ullman RN, GradCertPICU, MAppSci, PhD, Centaur Fellow
Alliance for Vascular Access Teaching and Research (AVATAR), Menzies Health Institute Queensland, Griffith University, Brisbane, Qld, Australia
School of Nursing and Midwifery, Griffith University, Brisbane, Qld, Australia
Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia

Sarah Northfield RN, BN, GradCertNursing (Cancer)
Alliance for Vascular Access Teaching and Research (AVATAR), Menzies Health Institute Queensland, Griffith University, Brisbane, Qld, Australia
Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia

Li Zhang BMed, PhD
Alliance for Vascular Access Teaching and Research (AVATAR), Menzies Health Institute Queensland, Griffith University, Brisbane, Qld, Australia

Gabor Mihala MEng, GC (Biostatistics)
Alliance for Vascular Access Teaching and Research (AVATAR), Menzies Health Institute Queensland, Griffith University, Brisbane, Qld, Australia

Nicole Gavin RN, BSc (Hons), MAdvPrac
Alliance for Vascular Access Teaching and Research (AVATAR), Menzies Health Institute Queensland, Griffith University, Brisbane, Qld, Australia
Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia

Claire M Rickard RN, PhD, FAAHMS, FACN
Alliance for Vascular Access Teaching and Research (AVATAR), Menzies Health Institute Queensland, Griffith University, Brisbane, Qld, Australia
School of Nursing and Midwifery, Griffith University, Brisbane, Qld, Australia
Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia

* Corresponding author
Tricia Kleidon, Lady Cilento Children's Hospital, 501 Stanley Street, South Brisbane,
Qld 4101, Australia
Tel: 0407 175 301
tricia.kleidon@health.qld.gov.au

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- Pilot randomised controlled design to enhance reliability using predetermined primary outcomes of feasibility.
- Use of computer-generated randomisation and allocation concealment will avoid risk of selection and allocation bias.
- Enhanced generalisability due to pragmatic design. PICCs will be inserted and cared for by general staff in two hospitals. Specialist teams or researchers will not undertake insertion and maintenance.
- Paediatric and adult patients will be recruited to enhance generalisability to both populations.
- An accredited radiologist and infectious disease specialist (blinded to group allocation) will act as outcome assessors and will be tasked with diagnosis of any vessel thrombosis or catheter-associated bloodstream infection, respectively.
- Type of PICC inserted cannot be blinded to clinical staff, patients, or research nurses (ReNs), as the experimental PICC and standard care PICC look physically different.

INTRODUCTION

Peripherally inserted central catheters (PICC) are integral to the treatment of acute and chronic illness. Yet premature device failure occurs in approximately 30% of cases, causing interruptions to treatment that can be life-threatening[1-3]. PICCs are used with increasing frequency in paediatric and adult patients as a 'safer' alternative to the insertion of more invasive centrally inserted central venous access devices[4,5]. The insertion of a PICC enables the delivery of medication in an outpatient setting, reducing the need for prolonged hospitalisation, which is mutually beneficial to the patient, family and healthcare facility[6]. Indications for PICC insertion in children and adults can be as simple as providing a more reliable form of venous access to the traditional peripheral intravenous cannula (PIVC) in patients with limited, and/or difficult venous access, and requiring medium-term intravenous therapy[7].

Peripheral intravenous cannulas are consistently reported to be one of the most painful and anxiety-provoking inpatient experiences[8]. In this situation, PICCs provide a much-needed alternative to the insertion of multiple peripheral intravenous cannulas[9]. Across age groups, PICCs are frequently used for the delivery of intravenous medications such as antibiotics and anti-cancer therapies, other medicines, fluids, nutrition and transfusions, and for frequent blood sampling. Though initially viewed as safer, cheaper and more durable than centrally-inserted central venous access devices[4,5], PICCs are not without complications and approximately 30% of PICCs fail before completion of treatment[3,10-14]. Premature PICC failure necessitates device replacement, which can negatively affect vessel health and preservation as

excessive use of the patients' veins creates a situation where venous depletion is possible, which can severely impact future treatment options. Similarly, delays to antibiotic and chemotherapy regimens reduce treatment efficacy and can adversely affect subsequent survival rates[6].

PICC failure can result from vascular, infective, or mechanical factors. Severe pain and swelling is an early indication of vascular complications to the vessel endothelium[15]. Serious catheter-associated bloodstream infections (CABSIs) have been reported to cause PICC failure in 37% of PICCs in hospitalised cancer patients[16,17] and other high-risk patients[18]. Mechanical complications include partial or total dislodgement of the PICC from the vein. Dislodgement occurs in 5–13% of PICCs[3,10,12,14], via 'drag' from multiple infusion tubes, or 'catching' on environmental structures, for example, clothing, wheelchair and bedrail[19,20]. Partial dislodgement can result in fluid leaking into tissues, which can lead to serious adverse complications[21]. Occlusive complications can be thrombotic (occurs when blood is not effectively cleared from within the catheter), non-thrombotic (occurs when incompatible medications mix inside the PICC), or compression of the PICC by an irritated, swollen vein wall[16]. PICCs are also susceptible to fracture due to thin walls. Occlusion with or without fracture occurs in 4–23% of PICCs[3,10,12,14].

PICCs have progressed from relatively simple, silicone-based catheters with a clamp to chemically engineered polyurethane with valves designed to reduce occlusion placed at the proximal or distal catheter hub. Numerous iterations to the design and use of materials to manufacture PICCs have occurred since their early inception in the 1970s. Traditional silicone PICCs are still used today, although less frequently. The move from silicone to polyurethane was largely due to the weakness of the silicone material[22,23]. Polyurethane is intrinsically stronger, withstanding pressures of 100 psi (pounds per square inch), compared to 50 psi with traditional silicone PICC. Initial polyurethane PICCs were associated with increased phlebitis (inflammation of the vein) due to trauma on insertion as a consequence of the stronger, more rigid material. Additionally, PICCs were traditionally inserted without the use of ultrasound and in areas of high flexion where the vein was easily palpated and easy to access using landmark technique. Newer generation polyurethanes have been developed with additives that increase conformability within the vein, such as third generation polyurethane with Carbothane™[24]. Further modernisation of PICC material involves the incorporation of anti-thrombogenic material (Endexo™). These PICCs claim to contain a 'non-stick' polymer, designed to reduce biofilm attachment and subsequent infection, as well as reducing the risk of occlusion and deep vein thrombosis due to the purported inability of thrombus attachment.

Valve technology was introduced to prevent occlusion by reducing blood backflow into the device after flushing to reduce the risk of blood products within the catheter. Valve design is either at the distal hub or proximal catheter tip and is pressure activated: the valve opens on high pressure during flushing and negative pressure during aspiration. The valve remains closed with normal venous pressure[25]. Despite the increased frequency in PICC selection, there are comparatively few studies examining the evolution of PICC design and the effect these changes have had on PICC survival. For these reasons, we designed a pragmatic pilot randomised controlled trial that has primary outcomes of feasibility.

METHODS AND ANALYSIS

Design

Two separate pilot RCTs involving PICCs in adult and paediatric patients will be commenced to provide information for the planning and justification of a future efficacy RCT; these pilot studies will inform any components of the future study that require modification, including the protocol, processes and outcomes. The study is referred to as Peripherally Inserted Central Catheter OutcoMes PolyurethAne veRsus Endexo: the PICCOMPARE trials, and was prospectively registered in the Australian and New Zealand Clinical Trials Registry (ACTRN12615001290583 and ACTRN12616001578493).

Study setting

The paediatric RCT will be conducted at the Lady Cilento Children's Hospital (LCCH), Brisbane, Australia, which is a level 6, specialist paediatric teaching hospital providing full-spectrum health services to children and young people from birth to 18 years of age. Referrals are received from throughout Queensland, Northern New South Wales and the Pacific Rim. The adult RCT will be conducted at the Royal Brisbane and Women's Hospital (RBWH), Brisbane, Australia, which is another level 6 hospital providing quaternary and tertiary referral services located at the Metro North Hospital and Health Service (MNHHS) Herston site. It provides more than one-tenth of all patient services in Queensland.

Participants

Patients booked to have an elective PICC insertion or urgent PICC insertion will be identified by the research nurse (ReN) who will screen patients daily for suitability to participate in the trial. Patients with an existing non-trial CVAD in situ that requires device replacement, either elective or due to failure, will also be approached for recruitment if they meet the inclusion criteria. In total, 220 patients will be recruited: 110 participants will be recruited from each site (allowing for potential 10% attrition). The aim of these two pilot studies is to test the feasibility of the definitive RCTs, rather than hypothesis testing. Thus, power level was not a valid consideration for sample size. Instead, the PICCOMPARE sample sizes are in accordance with recommendations by Thabane and colleagues[26] and Hertzog[27], to facilitate accurate estimates of effect size while minimising unnecessary costs, time and recruitment of future definitive study participants. Patients are eligible for enrolment if they meet all the inclusion criteria: require PICC insertion for fluid or medication administration; likely to remain an inpatient for > 24 hours; and able to provide informed consent. Exclusion criteria include: previous enrolment in the current study; current CABSI; and non-English speaking without an interpreter.

Interventions

Local clinicians established the intervention arms after considering current local practice, best available evidence, and the safety of the participants. The intervention arms for each PICC study have been tailored to the individual hospital's preferred PICC prior to trial. LCCH and RBWH routinely insert Cook™ Turbo-Ject Power-Injectable PICC. Bioflo™ with Endexo™ technology was chosen as the comparator due to the assumed benefit of reducing the risk of thrombosis and biofilm adhesion

OUTCOME MEASURES AND DEFINITIONS

Primary outcome:

Feasibility of conducting an RCT of the efficacy and cost-effectiveness of BioFlo compared with older generation polyurethane PICCs in the paediatric and adult population is the primary outcome. This will be established by composite analysis of elements of feasibility including: eligibility, recruitment, retention and attrition, sample size estimates, protocol adherence and missing data, as previously described by Lancaster and colleagues[28], Thabane and colleagues[26] and Hertzog[27].

Secondary outcomes include a composite analysis of all-cause PICC complications and failure. This will include:

- ***Infection***

– *Catheter-associated bloodstream infection (CABSI)*: A laboratory-confirmed BSI that is not secondary to an infection at another body site (excludes Mucosal Barrier Injury LCBSI), with PICC in place for > 2 calendar days on the day of the BSI (day of PICC placement being with PICC in place for > 2 calendar days on the day of the BSI (day of PICC placement being Day 1) and the PICC was in place on the date of the event or the day before, when all elements of LCBSI, were first present together (see CDC NHSN for full criteria)[29] confirmed by a blinded infectious disease specialist using de-identified clinical and microbiological data, *or*

- *Local infection*: Purulent phlebitis confirmed with a positive skin swab (> 15 colony forming units [cfu]) or PICC tip culture, but with negative or no blood culture[29], confirmed by blinded infectious disease specialist.

- ***Occlusion***

– ≥ 1 lumen cannot be flushed, aspirated, or resolved post-thrombolytic dwell[10].

- ***Fracture***

– Visible split in PICC material with leakage or radiographic evidence of extravasation or infiltration into tissue, causing removal[12].

- ***Venous thrombosis***

– *Suspected*: Removed as too painful for patient to tolerate[10], or
– *Confirmed*: Ultrasound- or venographically-confirmed thrombosed deep vessel (basilica, brachial, axillary or subclavian) at the PICC site in a patient with symptoms of thrombosis such as arm pain, swelling, redness, and tenderness at PICC site[10,30], or a symptomatic patient with a thrombus or fibrin sheath occluding ≥ 1 lumen at PICC removal[31].

Study procedures

The ReN will screen patients daily, obtain written informed consent and undertake randomisation. The ReN will liaise closely with the PICC insertion clinicians. Randomisation will be web-based via Griffith University https://www151.griffith.edu.au/random. Patient-level randomisation will be 1:1 ratio between groups with randomly varied block sizes and stratification by hospital site (LCCH vs RBWH) and PICC size (3fr, 4fr, 5fr). This will ensure full compliance with best practice standards for randomisation generation and allocation concealment until study entry. The project manager will undertake quality checks to ensure allocation integrity.

The type of PICC inserted is not amenable to blinding of patients, clinical staff or ReNs. There is no suggestion in the literature or practice that staff and patients favou one PICC over another, and we have no reason to believe that staff will not be consistent with follow through on the randomised device as the change will be noticeable. A statistician blinded to allocation will similarly undertake all analyses.

Data collection

Each participant will be visited on the day of insertion, and then assessed at least bi-weekly by the ReNs throughout the PICC duration. ReNs will collect data from electronic and other charts, and manually enter observations into a Research Electronic Data CAPture (REDCap) database (http://project-redcap.org/), accessed using a wireless tablet computer. Discharged patients will have follow-up data collected via outpatient clinics, hospital in the home service, or over-the-phone.

At enrolment, ReNs will collect demographic data to describe the participant group and enable comparisons to inform future generalisability. Data will also be collected regarding patient and device-related characteristics known to increase the risk of PICC failure. Variables to be collected will include age, gender, diagnostic category, existing infections, presence of stoma/wound/s, length of hospital stay, mobility, previous thrombosis, previous PICC, site of insertion, size of vessel (measured without tourniquet), quality of blood drawn and number of samples drawn, vessel access technique, number of attempts and experience of PICC inserter. Immediately or within 24 hours, ReNs will ask the staff member who inserted the study product to rate ease of insertion using an 11-point scale (0 = very difficult, 10 = very easy), and how many times they have previously used that study product. Within 48 hours of PICC removal, the ReN will collect data on: reason for removal including presence and type of failure if present; PICC dwell time; total number and type of set disruptions and infusates. Also within 24 hours, ReNs will ask the patient/parent about satisfaction and confidence with the study products on an 11-point scale (0 = completely dissatisfied, 10 = completely satisfied). At 48 hours post-PICC removal ReNs will collect microbiological and clinical data needed for infectious and microbiological outcomes, and confer with the blinded infectious disease physician to confirm CABSI. ReNs will collect data on: hospital length of stay and mortality. PICCs that remain complication-free at this time will be noted as non-CABSI/non-failures.

PICC procedure

Other than PICC type, all other PICC insertion, care and management will be standardised in accordance with local clinical practice guidelines[32]. This includes skin preparation with 2% chlorhexidine gluconate in 70% alcohol prior to insertion, ultrasound guidance for insertion, application of one drop of tissue adhesive at the exit site to assist haemostasis if necessary (applies to LCCH only), securement with sutureless securement device and simple or bordered polyurethane dressing and removal as soon as clinically appropriate. Catheter-to-vein ratio will be considered by the clinician inserting the PICC, the vein will be measured without tourniquet prior to inserting the PICC to ensure appropriate catheter-to-vessel ratios[33] are met to reduce the complication profile. The ReNs will coordinate and manage all insertion, management and removal care to ensure optimisation and standardisation of clinical practice.

Extensive education activities including use of insertion equipment will be provided to hospital staff to ensure consistency and protocol adherence. Clinical staff will take blood and PICC tip cultures on suspicion of infection, as per standard hospital and pathology protocols. Diagnosis of CABSI is by an independent, blinded infectious diseases specialist. Routine cultures are unnecessary, as they provide no added diagnostic value[34]. Similarly, ultrasound for the identification of symptomatic venous thrombosis will be requested by the clinical team co-ordinating the participants' care, with diagnosis made by an independent, blinded radiologist using standard department protocols. Protocol *violations* are defined as insertion of an incorrect or non-randomised PICC. As it is not feasible or clinically appropriate t change the product once inserted, any patients affected by protocol violations will not be included in the per-protocol analysis. All patients affected by protocol violations will have follow up data collected by ReNs for inclusion in the intention-to-treat (ITT) analysis.

Microbiology sub-study

A sub-study (purposive 20%; n = 20) will have the PICC tip examined by the semi-quantitative method. The removed PICC tips will be rolled back and forth on blood agar plates and incubated 37 degree under aerobic condition for 72 hours. Microorganisms will then be isolated and identified according to standard microbiology protocols. The PICC tip will be defined as colonised if the plate grows more than 15 colony-forming units (cfu). Blood cultures (if ordered by clinicians) from a peripheral vein and PICC lumens will be cultured and identified by Microbiology Pathology Queensland Central laboratory.

Reliability and validity

The reliability of the PICCOMPARE trials will be ensured through the adherence to the *a priori* study protocol[35]. Internal validity will be maintained by following the study protocol monitored by the Project Manager, with adherence to reporting safeguards to minimise bias. Use of computer-generated randomisation and allocation concealment will avoid risk of selection and allocation bias. The PICCs being trialled are not amenable to blinding of patients, family members, clinical staff or research staff. Radiological and laboratory staff assessing the CABSI and venous thrombosis outcomes will be blinded. With an ITT approach, all participants will be accounted for in the final analysis following randomisation[36]. The CONSORT Guidelines[37] including the checklist and diagram will be used to report the PICCOMPARE trials findings.

Statistical methods

Each pilot study will be analysed separately. Descriptive statistics will be used to ascertain the primary outcome of feasibility for the larger trial. All randomised patients will be analysed on an ITT basis. Comparability of groups at baseline will be assessed using clinical parameters. Incidence rates of PICC failure (per 1,000 device days) and PICC complication (per 100 devices) will identify the impact of each PICC type; group differences will be evaluated by calculating 95% confidence intervals and p-values. PICCs in situ after 12 weeks or at hospital discharge will be censored from analysis at this point. Kaplan-Meier survival curves (with log rank test) will compare PICC failure and complication over time. Secondary endpoints including dwell-time, thrombosis, occlusion, infection and safety will be compared between groups using parametric or non-parametric techniques as appropriate. In addition to group, multivariate regression (Cox) models will test the effect of patient and device variables associated with PICC failure, e.g., insertion site, vessel size, operator, tip position, side of insertion, dwell time, length of stay, diagnostic group, age, sex, mobility, co-morbidities and IV medications. Data cleaning of outlying figures, missing, and implausible data will be undertaken, and a random 5% sample of

source data re-entered and checked prior to analysis. Attempts to ensure all primary endpoint data is collected will be prioritised. A per-protocol analysis will assess the effect of protocol violations. P values of < 0.1 will be evaluated as indicating some evidence against a null hypothesis, and values < 0.05 will be considered statistically significant.

Estimating cost parameters

Trial costs will be collected as direct product costs (material costs) and healthcare resource utilisation (labour costs), including failure-associated costs using previously established cost estimates[38]. Health resource utilisation will be measured by assessing the staff time and equipment associated with PICC insertion[39]. Group differences will be tested using a non-parametric statistical test.

ETHICS AND DISSEMINATION OF RESULTS

Ethical and safety considerations

The trial has approval from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/15/QRCH/164) and Griffith University Human Research Ethics Committee (Ref No. 2016/077), and is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12615001290583 and ACTRN12616001578493).

Prior to providing consent to participate, adult patients and parents/legal guardians of children will be given an Information Sheet, time to read and fully comprehend, and an opportunity to ask questions. Children older than six years of age and developmentally appropriate will be offered a Youth Assent form. All children will be provided with information regarding the study and given the opportunity to provide assent for participation. Withdrawal from the study will in no way affect the care patients receive from the hospitals. Participant confidentiality will be ensured and anonymity guaranteed. Only aggregate data will be published and data will be stored according to National Health & Medical Research Council guidelines[40].

Trial status

Recruitment of patients to the paediatric PICCOMPARE trial began in April 2014. Recruitment of patients to the PICCOMPARE adult study will commence February 2017. It is expected that recruitment will be completed for both pilot studies by December 2017.

CONCLUSION

PICC failure results in serious consequences for the patient, family and healthcare system. Interruption to necessary treatment results in the inability to administer necessary therapies. Furthermore, the insertion of a replacement device after PICC failure becomes more difficult and negatively impacts a patient's vasculature. Patients suffer significant related morbidity and millions of health dollars are wasted through treatment of complications and extended hospital days. Newer PICC technology might mitigate some of the factors related to PICC failure. This pragmatic, multi-centre, pilot RCT will help to determine the feasibility of undertaking a large efficacy study to assist clinicians in their device choice for their patient population.

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COMPETING INTERESTS STATEMENT

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