# Peripherally inserted central venous catheter insertion site and complication rates in neonates: a randomized controlled trial

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## 1. Background and rationale

### 1.1. PICC lines as 'life lines' in neonates

Peripherally inserted central venous catheters (PICCs) provide lasting venous access to deliver total parenteral nutrition (TPN) and medications for neonates receiving intensive care, especially in very low-birth-weight infants.[1] In neonates, PICC lines are commonly inserted at the basilic, cephalic, and axillary veins in the upper extremity, the great saphenous and popliteal veins in the lower extremity, and the temporal and posterior auricular veins in the scalp.[2] The incidence of PICC associated complication rates in literature varies from 27 to 42%.[3, 4, 5] The common complications resulting in removal of PICCs include mechanical complications such as line infiltration, line occlusion, thrombosis, [3, 4, 5] central line-associated bloodstream infection (CLABSI),[2–6] and life-threatening complications such as pericardial effusion and temponade[7–9] and pleural effusion.[10, 11]

### 1.2. PICC related complication reports with site of insertion

Usually the site of insertion is chosen based on the inserter's preference and accessibility of veins rather than incidence of complications. In adult literature, it has been reported that lower extremity PICCs are associated with a higher risk of infection than upper extremity PICCs, and it is recommended to avoid femoral sites in adults.[12,13] However, studies in pediatric patients have demonstrated that femoral catheters have a low incidence of mechanical complications and might have an equivalent infection rate to that of non-femoral catheters.[14,15] In neonates, only a few retrospective studies have reported complication rates based on the site of insertion with conflicting results.[16-19] In a retrospective study, Hoang et al[16] reported that upper extremity PICCs had significantly higher rates of *coagulase negative staphylococcal* septicemia and cholestasis as compared to lower extremity PICCs in neonates. Wrightson[17] reported no difference in the overall complication rate between upper and lower extremity PICCS (27% vs 21%). Presumed sepsis was the most common complication requiring PICC removal. Both studies included infants of all gestational ages (including term infants) and all the PICCs inserted. It is possible that a higher number of PICCs inserted in a single baby may increase the complication rates. Ozkiraz et al[18] also reported no difference in complications between upper and lower extremity PICCs in very low-birth-weight and extremely low-birth-weight infants. Some studies in preterm infants recommended avoiding PICCs in the lower limbs, especially at the femoral site because of a high incidence of sepsis and thrombosis.[2,18] Our retrospective study in Calgary noted that the overall rate of catheter-related complications resulting in PICC removal was not significantly different between upper and lower extremity PICCs.[19] However, there was a 2.4-fold increase in odds of line infiltration among upper extremity PICCs, especially on the right side. Line occlusion was more common in lower extremity PICCs.

### 1.3. Non-central catheter tip position associated with complications

When the tip of PICC is not at the superior or inferior vena cava, it is called non central catheter tip position. The mid-clavicular tip position of central lines is more commonly associated with line infiltrations.[4] In a study by Jain et al,[4] non-central PICCs developed more complications in less time, leading to non-elective catheter removal. Similarly, Racadio et al

reported a sevenfold increased risk of complications when the catheter tip was non-central in pediatric populations.[20] Use of high-osmolar TPN solutions infusing through PICC lines might have contributed to the infiltrations,[19] especially if the catheter tips were non-central (midclavicular location). The details of these potential factors are not available from retrospective studies. Likewise, catheter tip position has not always been documented in retrospective studies.[19]

**1.4.Thrombosis as a complication of PICC lines**

In adults, it is reported that spontaneous deep venous thrombosis occurs more commonly on the left side as compared to the right side.[21]However, in neonates, there is no uniform policy to assess thrombosis. [19] It has been observed that lower extremity PICCs had a higher rate of major venous thrombo-embolism especially in neonates with intra-abdominal surgeries.[22] Likewise, infiltration and phlebitis were commonly seen with lower limb PICCs in neonates with gastroschisis during silo reduction and within 5 days of abdominal closure.[23]

**1.5. Relation of catheter insertion site to tip position**

Proximity of insertion site to catheter tip destination has been suggested to be a factor against PICC-related complications. Panagiotounakou et al observed that PICCs inserted through axillary veins were associated with 12 times less complications and were 7 times electively removed due to achievement of full enteral nutrition as compared with the PICCs inserted through forearm veins due to proximity of insertion site to catheter tip destination.[24] Tsai et al reported that culture-proven sepsis was common with femoral PICCs, whereas non-infectious complications were common with non-femoral PICCs.[25]

**Rationale for the study:**

There are no prospective or randomized clinical studies in the literature that have looked at the site of PICC insertion and complication rates in neonates. Earlier retrospective studies also included all PICC lines irrespective of the timing of insertion or number of catheters used on an individual patient. Retrospective studies lack pertinent information to determine why the site was chosen and details of complication types. A well-designed prospective randomized clinical trial is required to conclusively establish if PICC site placement is a factor affecting complications that necessitate non-elective removal of the device. Moreover this study will also help in understanding the specific complication such as thrombosis related to PICC line.

## 2. Research Question

In neonates who require PICC placement as a part of their care in NICU, does complications following PICC insertion resulting in early (non-elective) removal of catheter differ based on the site of insertion?

P: Neonates admitted to the NICU

I: Lower extremity PICCs

C: Upper extremity PICCs

O: Any complication necessitating non-elective removal of lines

T: During the period of PICC insertion

**3. Study hypothesis:**

We hypothesize that there is an association between the site of PICC insertion and the complications necessitating PICC line removal non-electively and complications rates are different between upper extremity and lower extremity PICCs.

**4. Study objective:**

i) To examine whether the complications following PICC insertion resulting in early removal differ based on the site of insertion

**5. Methods:**

**5.1. Study design**: Parallel group, prospective, randomized controlled trial

**5.2. Description of population**: All neonates admitted to the level III neonatal intensive care unit (NICU), Calgary, Canada (i.e. Foothills Medical Centre (FMC) and Alberta Children's Hospital (ACH), will be eligible for the study and will be screened for participation. Randomization will be done once inclusion criteria are met, in the absence of exclusion criteria and once informed consent is obtained.

**5.3. Inclusion criteria:**

- Neonates of all gestational ages admitted to Foothills Medical Centre and Alberta Children's Hospital NICU
- PICC line insertion planned as part of NICU care
- Venous access available in both upper(above umbilicus) and lower body

**5.4. Exclusion criteria:**

- Local infection at potential site of insertion
- Hemangioma, lymphangioma or malformations in the region of insertion
- Major chromosomal anomalies

**5.5. Randomization**:

Eligible infants will be randomly assigned for upper extremity or lower extremity PICC insertion using an allocation ratio of 1:1. We will use blocked randomization of varying block sizes in multiples of two. The investigators will be blinded to the block sizes; but the block sizes will ensure appropriate balance between both arms. Infants will be stratified into two groups based on the gestational age (≤ 32 weeks, >32weeks). Randomization will be performed using computer generated software once eligibility is confirmed and informed consent is obtained. A unique patient identification number and the randomisation sequence will be generated.

**5.6. Interventions:**

PICC insertion attempts will be made by certified health care providers including transport nurses, nurse practitioners and physicians using standard clinical practice guidelines. A maximum of two attempts will be allowed in the designated region, following which further attempts will be considered in the non-designated region if the inserter is confident of success. Number of attempts at insertion and sites of attempts will be recorded as per unit protocol. After the catheter is inserted, catheter tip position will be confirmed by radiograph with the limbs in standard position as per unit protocol, and repeat radiographs will be taken if there is a manipulation. As per unit protocol, the catheter inserter will record the details of the procedure, the type of catheter used, and position of catheter following radiographic confirmation in the progress note of each infant's medical chart. Similarly, the bedside nurse also documents this information in the nursing chart/Metavision. In addition, the inserter will fill out a one-page PICC line tracking sheet for all the lines which includes details such as the indication, date of insertion, site of insertion, catheter tip position, and any complications during insertion. Once the

PICC is removed, the bedside nurse will complete the PICC tracking sheet, filling in the date and the reason for removal of the line.

The clinical goal is to place the catheter tip in the superior vena cava or inferior vena cava, but outside the right atrium. A catheter tip lying beyond the medial end of the clavicle and up to 1 cm at the junction of right atrium and superior vena cava is considered optimal for upper extremity. PICCs with the catheter tip located in the inferior vena cava below the diaphragm are considered optimal for lower extremity PICCs. Heparin will be infused in all PICCs as per standard unit policy. All catheters will be removed either after completion of intravenous therapy or earlier if they develop complications. In all babies an ultrasound will be performed within 72 hours of PICC line removal by neonatologists trained to perform point of care ultrasound, looking for the presence of an occlusive thrombus. If one is detected, consultation to radiology and hematology will be requested as per unit protocol.

**6. Study Outcomes:**

**6.1. Primary outcome:**

Primary outcome is the presence of any complication which necessitates PICC removal. This includes mechanical, central line associated blood stream infections (CLABSI) and major life threatening complications.

i) Mechanical complication will be considered present if there is a line infiltration, occlusion, phlebitis, and dislodgement, resulting in removal of PICC. [19]
ii) Line infiltration will be defined as extravasation of fluid into soft tissue around the region of the catheter tip. [19]
iii) Line occlusion will be defined as inability to infuse fluid, resulting in removal of line.[19]
iv) Phlebitis will be defined as presence of a linear red streak developing along the superficial veins from the catheter insertion site.[19]
v) Line associated thrombosis will be defined as ultrasound proven evidence of an occlusive thrombus in an anatomic location in proximity to the site of PICC.
vi) CLABSI will be defined according to Center for Disease Control definitions [26], that is, (1) confirmed primary bloodstream infection with (2) one of following clinical signs of infection (fever, hypothermia, apnea, or bradycardia) and (3) presence of central catheter at the time of or within 48 hours before the onset of the infection.
vii) Major life-threatening complications will include pleural effusion, pericardial effusion and cardiac tamponade, retroperitoneal extravasation etc

**6.2. Secondary outcome**: Secondary outcome will be time to complication post insertion. This will be defined as the interval between PICC line insertion and first detection of complication post insertion, expressed in days.

**7. Statistical analysis:**

**7.1. Sample size calculation:**

Based on our previous retrospective study, the rate of PICC complication resulting in removal of PICC was 30%.[19] In order to find a clinically important difference of 10% between PICCs inserted through upper extremity and lower extremity, a sample of 153 infants in each group will be required at 80% power and alpha error of 5%. We will recruit 320 infants. . Approximately 200 -250 PICCs are inserted per year in Calgary NICUs. We expect to complete recruitment over 18 month's period.

### 7.2. Statistical methods:

Data will be analyzed using intention-to-treat analysis. Baseline demographics of the study population will be described using descriptive statistics. Data will be checked for normality. Categorical variables will be presented as counts and percentages and continuous variables as mean and standard deviation or median and inter-quartile range if data are not normally distributed. Primary outcome, which is the presence of any complication, necessitating PICC removal, is a binary outcome where we will use chi-squared test or Fisher exact test. Event rates, relative risk and 95% confidence intervals will be reported for primary outcome. Secondary outcome, which is the time from PICC insertion to development of complication, is a continuous outcome for which two sided independent samples t-test or Mann-Whitney U test, depending on if the data is normally distributed or not. Standard deviation and 95% confidence interval will be reported for continuous outcomes. We will also calculate time to complication post insertion as median time. We will also do multivariate logistic regression analysis to examine the association of PICC site and complication rate after adjusting for gestational age, day of PICC insertion and illness severity score. P-value $<0.05$ will be taken as significant. Stata 15 will be used for the analysis.

## 8. Trial administration:

**8.1. Clinical Site:** This multicentre study will be conducted at the Neonatal Intensive Care Unit, in Foothills Medical Center and Alberta Children's Hospital NICU, Calgary, Canada

**8.2. Steering Committee and Local Operations Group:** The steering committee will consist of two neonatologists, two transport nurses, one Clinical Trials Coordinator and one nurse clinician. Along with these, there will be a study physician committed to the trial and a research assistant responsible for the daily conduct of the trial including recruitment, informed consent, administration of intervention, data collection, and in-servicing of relevant NICU staff.

**8.3. Data Safety Monitoring Board (DSMB):** This committee will be made up of two separate neonatologists, a statistician, and a unit manager, who will be blinded to the two groups. They will function independently from the study investigators. Once half the intended recruitment is reached, an interim analysis of clinical outcome data for efficacy and data analysis for expected and unexpected adverse events will be done. The DSMB will recommend termination of the trial for statistically significant ($p<0.001$) differences between the intervention groups with respect to PICC related complications, mortality, or serious unexpected adverse events. Results of the interim analysis will not be disclosed to investigators or study participants but will be published along with the DSMB's recommendations upon completion of the trial.

**8.4. Data Collection:** All data collection will be done with the help of a research assistant, supervised by a physician who is committed to the study. The study physician will check the data collection forms for completeness of data and fill each form separately. The study data will be collated and entered into the study database for analysis. Completed data collection forms and all the reporting forms will be securely locked in a closed cabinet in the study Principal Investigator's office at FMC.

**8.5. Study Monitoring:** The specific committee will ensure that all study procedures are in compliance with good clinical practice. It is imperative that the study proposal and all the amendments will be approved by the local Research Ethics Board.

**8.6. Data Quality Assurance:** Baseline infant demographics, details of PICC insertion and maintenance will be obtained from patient chart and electronic medical record. X-ray for PICC position and ultrasound reports and images to screen for thrombus will be available in the

IMPAX. Details of infusing solution through the PICC line as well as laboratory parameters will be available in the electronic medical record.

**8.7. Regulatory Approval:** All the interventions used for the conduct of the study has been approved by Health Canada, hence no special permissions are required.

**8.8. Subject Confidentiality:** Appropriate measures will be taken to maintain subject confidentiality. Although hospital database will have personal identifiers, only the random ID will be available in the research database. Privacy of electronic records will be maintained in the secure hospital server. Since the intervention cannot be blinded, the most responsible physician and the research team will know about any adverse event which occurs.

**8.9. Retention of Records:** As per Health Canada and local Research Ethics Board, paper records will be maintained for 5 years and electronic records for 7 years before destroying.

**8.10. Documentation of Protocol Deviations:** Research staff will be instructed to report all protocol violations in a particular reporting form created for the purpose.

**9. Ethical Considerations:**

This study will be conducted in accordance with the Good Clinical Practice guidelines and local Research Ethics Board requirements. Parents will act as surrogate decision makers for the patient.

**10. Feasibility and limitations:**

Major limitation of the study is the large sample size. We expect around 320 babies to be enrolled to see an effect. In our retrospective study[19], there were around 900 first time PICCs over a period of 5 years from 2006- 2010, which gives an average of 180-200 PICCs per year. Accordingly, it will take about 1.5-2 years to finish the trial.

**11. Impact of the study:**

The results of this trial will help to figure out if there is an association with increased complication rates when PICC lines are inserted through upper or lower extremities. If there is a significant difference detected, it will definitely guide the inserter to select the site with fewer complications, especially in a neonate with first time PICC insertion, rather than base the choice of site of insertion on personal preference and venous accessibility.

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