**Comparison between Mathematical Formula and Direct Measurement for Insertion of Peripherally Inserted Central Catheter (PICC) in Neonates**

**1. INTRODUCTION**

**1.1 Background**

A PICC (peripherally inserted central catheter) is a catheter in which the tip resides in a central vein via percutaneous insertion from a peripheral vein. It was introduced for the care of preterm infants in 1980. Neonatal patients often require long-term vascular access for the delivery of prolonged parental antibiotic treatment, total parenteral nutrition or blood product infusions. A neonatal PICC can be inserted at the patient's bedside and it can remain in place for several weeks. The small diameter of its lumen is ideal for the extremely small neonate. The tip location of PICC should be checked by an X-ray after the procedure.

However, the placement and maintenance of peripheral intravenous catheters in preterm infants is difficult and can become a challenge for clinicians. An umbilical venous catheter (UVC) is commonly used in the first week after birth as a central catheter in sick infants, however this is typically replaced with a PICC for long periods of intravenous catheter maintenance, as the complications of a UVC are closely related to the duration of its use.

The complications of PICC placement have been previously reported as infection, thrombosis, phlebitis, bleeding and misplacement. The complication rate of PICCs is associated with the location of their tips. Centrally placed catheter tips are associated with fewer complications compared with non-centrally placed catheter tips (Jumani, Advani et al. 2013). Therefore, the tip location of PICC is an important factor in reducing the complication rate of PICC.

In this study, the data of babies who had PICC inserted during their hospitalization in NICU HUSM were evaluated. Comparison will be made regarding measurement of PICC length inserted. Current measurement practice in NICU HUSM is by direct measurement. We will compare this with measurement using mathematical formula developed by I-Lun Chen et al published in July 2018 (Chen, Ou-Yang et al. 2019).

**1.2 Justification to Conduct the Study**

PICC insertion is important especially for preterm babies, to prevent frequent line insertion usually for total parenteral nutrition and medications. Therefore, it is important to make sure the PICC insertion is safe, with minimal complication. As mention, complications can be reduced by correct placement of the tip of PICC. The reason of conducting the study is to determine the best method of PICC insertion length measurement; comparing direct measurement and mathematical measurement.

**1.3 Literature Review**

The formula for PICC measurement used in this study was developed in July 2018 by I-Lun Chen et al (Chen, Ou-Yang et al. 2019). Therefore, there is limited literature review comparing PICC insertion with direct measurement and mathematical measurement.

There is one study done in adult population by Philip Lum et al in 2004 at a cancer centre in Houston, Texas. It is a prospective observational study of three percutaneous insertion sites including PICC, subclavian catheter and jugular catheter. Formula based height measurement was used to determine catheter length. A total of 382 patients included in the study. Out of that, 373 (97%) of them were successfully placed with the tip in distal/ optimal location, based solely on the calculated formula-based measurement guide for determining catheter length. For PICC, total of 134 catheterizations done. Results show that 129 (96%) of the catheter tips were within distal superior vena cava (within carina and atrio-cava junction). This study concluded that the tailored-fit formula to individual patient height is a reliable tool to predict central venous catheter length (Lum 2004).

Another study done in 2005, by Kim et al, a team of paediatric anaesthesia, to determine accuracy of central venous catheter placement in infants less than 5 kg who were scheduled for elective repair of ventricular septal defect or atrial septal defect. CVC is inserted infraclavicular approach, subsequently SVC-RA junction was observed using transesophageal echocardigraphy. Distance from skin puncture to SVC-RA junction is measured. By using linear regression, a formula using height and weight was developed. Out of 50 patients, 49 of them (98%) the CVC was placed in the SVC above right atrium when CVC length measured using the formula. (Yoon, Shin et al. 2005)

In a prospective observational study in paediatric patients, Andropoulos et al, 456 central venous catheters that were inserted at right internal jugular or right subclavian veins and the catheters position was confirmed using chest radiograph. By using linear regression, an equation using height of the patients were developed. The used of this formula predicted that 94.0% (95%CI, 88.0%–97.5%) of CVC inserted from right subclavian vein terminated at Superior vena cava and 99.4% (95%CI, 97.8–99.9%) of CVC inserted at right internal jugular terminates at superior vena cava (Andropoulos, Bent et al. 2001).

 Hyun Hwan Cho et al has developed a formula for PICC length according to height in adult population through a retrospective study. A total of 124 patients was inserted with PICC through the right basilic vein under fluoroscopy were included. Relationship between PICC length and patient height are analyzed using linear regression and was found to be significantly correlated (p<0.01) (Cho, Jeon et al. 2012).

 A retrospective observational study in paediatric patients, Fricke et al, has placed 843 PICCs in 698 patients according to clinical protocol, by a specialized team of PICC nurses and interventional radiology technologists, and the initial PICC tip location was then determined by means of spot fluoroscopy. All catheters were then manipulated with intermittent fluoroscopic guidance to achieve a final central position. A chi-square test was used to compare initial and final PICC tip locations according age, catheter size, accessed vein, and need for radiological assistance. Out of 843 PICCs, 723 (85.8%) required additional manipulation (Fricke, Racadio et al. 2005).

**1.4. Research Hypothesis**

We hypothesized that determination of the length of insertion of PICC in neonates using mathematical formula based on body measurement has higher successful rate with lower rate of complication compared to direct measurement.

**1.5. General Objective**

To compare the outcome of mathematical formula versus direct measurement for length of PICC insertion

**1.6. Specific Objective**

1. To compare the proportion of successful PICC insertion when using mathematical formula versus direct measurement.

2. To compare the proportion of complicated PICC when inserted using mathematical formula versus direct measurement.

3. To compare the rate of removal of PICC when inserted using mathematical formula versus direct measurement in neonates

4. To compare the mean number of PICC readjustment when PICC is inserted using mathematical formula versus by direct measurement

**2. METHODOLOGY**

**2.1. Trial Design**

Two centres, parallel design, randomised control trial (RCT) with one to one allocation ratio. Participants will be divided into control and intervention group.

Assessed for eligibility (n=…)

Excluded (n=…)

Randomised (n=…)

Group A: Intervention (n=…)

Group B: Control (n=…)

Figure 1: Study flow chart

**2.2. Eligibility Criteria for Participants**

Participants of the study are neonates admitted in NICU of participating centres with PICC insertion.

* + 1. **Inclusion criteria for the study;**
1. Infants weigh equal or less than 1500g admitted to NICU that require PICC insertion in the participating NICUs within the study the period
	* 1. **Exclusion criteria for the study;**
2. Congenital anomaly that is expected to interfere with study outcome as listed;

-Orthopaedic problems: Arthrogryposis multiplex congenita, fixed congenital talipes equinovarus, development dysplasia of the hip (DDH), skeletal dysplasia,

-Chromosomal aneuploidy or genetic disorders : Any recognized or unrecognized dysmorphism , i.e. Down Syndrome, Patau Syndrome, Edward Syndrome, Single gene or polygenic defects, ie: Cri-du chat, Di George syndrome, Prader Willi Syndrome etc

1. Patient with vascular anomaly
2. Hydrops Fetalis
3. Asymmetrical Small for Gestational Age neonates

**2.3. Study Period/Area**

The study will be conducted in Neonatal Intensive Care Unit (NICU) at Hospital USM, Kubang Kerian Kelantan and Sultan Ahmad Shah Medical Centre (SASMEC). Hospital USM is a teaching hospital in Kubang Kerian, Kelantan, a state in Malaysia where majority of its population are Malays from different socio-economic background. The Neonatal Intensive Care Unit provides level 1 to level 4 intensive care to neonate patient and received referral from all parts of Kelantan and all over the country. IIUM Medical Centre NICU The study is planned to be conducted in the period between 1st December 2020 to 1st December 2021.

**2.4. Intervention**

Neonates who fulfilled inclusion and exclusion criteria will be assigned randomly into either two groups. All PICC that will be inserted for any reason either for total parenteral nutrition, for medication or inotropes will be included in the study. Group A will be the intervention group who will use mathematical formula. Group B will be the control group who will use direct measurement. All infants will have PICC inserted into the **right antecubital fossa**. **Vygon Premicath 1 Fr PICC** with the maximum length of 20 cm will be inserted in all the infants. For neonates randomized to Group A, the length of PICC insertion will be based on the formula;

Length (cm) = -1.45 + (0.36 x body length (cm))

Infants in group B will have the length of PICC based on direct measurement of the length between the PICC insertion site to sternal notch. All PICC will be inserted by a well-trained medical officers working in NICUs with at least one year experiences in PICC insertion. All the medical officers (MO) will be trained on the correct method to measure the length from the insertion site to the sternal notch. Inter and intra-observer reliability of the measurement will be assessed and repeat training session will be conducted if there is a poor reliability. For inter-observer reliability, we will use Bland-Altman plot analysis. Two MOs will be asked to measure the PICC insertion length of an infant. The procedure will be repeated on 10 infants. The difference of the two paired measurements is plotted against the mean of the two measurements. We will accept if all the plot lies within 95% CI of agreement limits. We will be using correlation analysis to determine intra-observer reliability. Ten babies and a random MO will be chosen. The MO will measure the insertion length of the PICC twice within 6 hours period and correlation coefficient (r) value will be measured. ‘r’ value of >0.8 is acceptable. Other steps of PICC insertion including the type of antiseptic solution, the dressing that will be used and post insertion care and maintenance will be according to the standard care in NICU.

For standardisation of the length measurement of the infants, we will use the same scale in both centres. Length is measured from tip of head until the bottom of one of the heel in lying position. All nurses working in all the participating NICUs will be trained on the correct method of length measurement. Similar intra and inter-observer reliability assessment will be conduct after the training session. Training session will be repeated until optimal reliability is achieved.

**2.5. Outcomes**

The primary outcome of this study is the proportion of successful PICC insertion; defined as the correct placement of PICC tip without the need for readjustment. This will be assessed by a designated radiologist that were blinded from the infant group allocation by reviewing the chest radiograph. Correct placement is confirmed if the catheter tip resides within the superior vena cava but above the level of T4 (Powls 2018). Outcomes will be divided into two categories; correctly placed or incorrectly placed PICC.

Secondary outcomes include the proportion of PICC that develop any complication attributable to the initial misplacement within two weeks of insertion, the rate of removal of PICC due to complications, and the mean number of PICC readjustment when PICC is inserted using mathematical formula compared to by direct measurement. The complications include arrhythmia, thrombosis, pleural and pericardial effusion, extravasation, catheter rupture, and catheter displacement. These outcomes will be measured by a neonatologist managing the infants in the NICU that is blinded from the randomization.

**2.6. Sample Size**

Sample size is calculated using PS-Power software version 3.1.6. for dichotomous outcomes.



In a previous study, proportion of correctly place PICC with the direct measurement, p0 was 0.26 (Chen, Ou-Yang et al. 2019). We wish to detect a proportion of outcome with intervention of 0.60 (p1 = 0.60), we will need to study 32 subjects in each group to be able to reject the null hypothesis that the proportion between the groups are equal, with the power of study 0.80. The Type 1 error probability associated with the test of this null hypothesis is 0.05. Taking into accounts 10% drop rate, total sample size required is 36 in each group.

**2.7. Research Tools**

Direct measurement of PICC length insertion will be measured from insertion site, to sternal notch for upper limb, and to umbilicus for lower limb. Measuring tape prepared bedside in NICU will be used to measure the distance.

The placement of PICC will be confirmed by imaging. Portable X-ray (Brand Shimazu) will be used instead of non-portable, because neonates who need PICC insertion are usually not very stable for transfer.

Research Proforma;

|  |  |
| --- | --- |
| **Patient ID** |  |
| **Date of insertion** |  |
| **Gestational age** |  |
| **Chronological age** |  |
| **Weight**  |  |
| **Length**  |  |
| **Gender** |  |
| **Purpose of insertion** |  |
| **Site**  |  |
| **Name of the vein** |  |
| **Catheter size**  |  |
| **Length of insertion** |  |
| **Vital sign**  | **BEFORE** | **1 HOUR AFTER** |
| HR |  |  |
| SPO2 |  |  |
| BP |  |  |
| **PICC insertion (successful/ satisfactory no need adjustment/ need readjustment)** |  |
| **Presence of complications;** | **YES** | **NO** |
| Arrhythmia  |  |  |
| Thrombosis |  |  |
| Pleural and pericardial effusion |  |  |
| Extravasation  |  |  |
| Catheter ruptured |  |  |
| Catheter displacement |  |  |
| Catheter removal (yes/no)State reason if YES |  |
| Number of readjustment |  |

**3. RANDOMISATION**

**3.1. Sequence Generation**

No sampling will be used in this study. All infants admitted that fulfilled the inclusion and exclusion criteria will be included in the study. The random sequence will be generated by a research coordinator who is not involved in the recruitment of patients, neither in the data collection nor care of the NICU patients using variable block randomization known only to that person.

**3.2 Allocation Concealment Mechanism and Implementation**

Patients will be recruited by the investigators, and only after inclusion in the study, consecutively numbered, sealed and opaque envelopes, carrying the allocation number will be opened. This number will determine the participant’s group allocation.

**3.3 Blinding**

The outcome assessor, nursing staff, and family were blinded from patient’s group allocation.

**3.4 Statistical Methods**

Data will be entered and analysed using SPSS version 24. The demographic and numerical data will be presented by mean (SD) and median (IQR) according to data distribution. The categorical data will be expressed as number and percentage. P-value ≤ 0.05% will be considered statistically significant. Chi Squared Test or Fisher-exact test will be used to compare the proportion of successful PICC insertion, the proportion of catheter that end up with complication attributed to the misplacement of the catheter or the readjustment procedure, and the proportion of catheter removed due to complication. Independent t-test or Mann-Whitney Test will be used to compare the mean number for readjustment attempted in both groups depending on the distribution of the data.

**4. RESULTS**

**4.1. Data Collection Method**

Data will be collected using a specific research data collection form that will be kept in a research folder not accessible to anyone apart from the research team. Every steps in PICC insertion will be documented together with details description on the method of insertion length measurement, size of the catheter, and the exact site and length of insertion of the PICC. Any immediate and post insertion complication such as arrhythmia and trauma and daily monitoring and assessment for development of delayed complications in the next two weeks post PICC insertion will also be documented by the investigator. Only research researchers can access the data to ensure confidentiality and to prevent bias. Data will be presented as grouped data and will not identify individual subject. Unit of analysis of this study is the recruited infant.

**4.2. Baseline Data**

**Table 1: Baseline demographic data**

|  |  |  |
| --- | --- | --- |
| **Characteristic**  | **Frequency, n(%)** | **p-value** |
| **Formula**  | **Direct measurement**  |
| \*Gestational age (week) |  |  |  |
| \*Chronological age (day) |  |  |  |
| \*Weight  |  |  |  |
| \*Length  |  |  |  |
| Gender-male-female |  |  |  |
| Name of the vein-Basilic-Brachial-Cephalic |  |  |  |

**\*Mean (SD) or Median (IQR)**

**4.3. Dummy Tables**

**Table 2: Outcomes of PICC insertion**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Frequency, n(%)** | **p-value** |
| **Formula**  | **Direct measurement**  |
| Successful PICC insertion |  |  |  |
| Type of complication |  |  |  |
| Arrhythmia Yes No |  |  |  |
| ThrombosisYes No |  |  |  |
| Pleural and pericardial effusionYesNo |  |  |  |
| ExtravasationYesNo  |  |  |  |
| Catheter displacementYesNo |  |  |  |
| Catheter RuptureYesNo |  |  |  |
| Extravasation  |  |  |  |
| Catheter electively removedYesNo |  |  |  |
| \*Number of readjustment |  |  |  |

\*Mean (sd) and median (IQR)

**5. ETHICAL ISSUES**

**1.      Subject vulnerability**

The participants of this study are newborn babies. By definition they belong to the most vulnerable of research participants. They cannot make decisions for themselves and are dependent on their parents. Parental written informed consent will be taken before babies are included in the study. The nature of the intervention carries very minimal risk. It is likely that the malposition of the catheters will be less. Even if it does not improve the position of the catheters effects of malpositioned catheters will be limited by monitoring of the position within 1 hour after placement of the catheter and readjustment if necessary.  No severe malposition or increased risk of perforation is expected. No extra blood taking or extra radiological exposure other than the routine care is involved in the study procedures. The babies are under the care of the doctors involved in the study. During the consent process extreme care will be taken to ensure that the participation in the study is completely voluntary, reassuring the parents, that if they do not participate in the study, their baby will still receive proper care.

**2.      Declaration of absence of conflict of interest**

The only conflict of interest is that the researchers are also involved in the care the baby. This will be addressed as stated in the last paragraph under ‘vulnerability’.

**3.      Privacy and confidentiality**

All forms are anonymous and will be entered into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the babies individually.

**4.      Community sensitivities and benefits**

No community sensitivities are anticipated. If the results show better outcomes, they may contribute to better care of babies in the future.

**5.      Honorarium and incentives**

No honorarium or incentives will be provided.

**6.      Other ethical review board approval**

Ethical approval will be sought from the following committees: MREC (KKM), IREC (SASMEC)

Applications to the other committees will be made only after JEPeM approval has been obtained.

**6. GANTT CHART**

|  |  |  |
| --- | --- | --- |
| Research activities | 2021 | 2021 |
| J | F | M | A | M | J | J | O | M | A | M | J | J | O |
| Proposal submission and ethical approval application |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data collection |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data analysis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Report writing |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Study completion |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Submission and publication of manuscript |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**7. FUNDING**

This research received research grant from Research Medical Council, IIUM

**8. DECLARATION OF CONFLICT OF INTEREST**

The researchers and all involved directly with the study has no conflict of interest.

**9. REGISTRATION**

This clinical trial will be registered to ANZCT Registry once ethical clearance received.

**REFERENCE**

1. Andropoulos, D. B., et al. (2001). "The optimal length of insertion of central venous catheters for pediatric patients." Anesthesia & Analgesia **93**(4): 883-886.

2. Chen, I.-L., et al. (2019). "The equations of the inserted length of percutaneous central venous catheters on neonates in NICU." Pediatrics & Neonatology **60**(3): 305-310.

3. Cho, H. H., et al. (2012). "A new formula to estimate the length of right upper extremity vein

 from elbow crease to carina calculated by peripherally inserted central catheter insertion through

 right basilic vein puncture." Journal of the Korean Society of Radiology **66**(3): 229-233.

4. Dell, R. B., et al. (2002). "Sample size determination." ILAR journal **43**(4): 207-213.

5. Fricke, B. L., et al. (2005). "Placement of peripherally inserted central catheters without

 fluoroscopy in children: initial catheter tip position." Radiology **234**(3): 887-892.

6. Jumani, K., et al. (2013). "Risk factors for peripherally inserted central venous catheter

 complications in children." JAMA pediatrics **167**(5): 429-435.

7. Lum, P. (2004). "A new formula-based measurement guide for optimal positioning of central

 venous catheters." Journal of the Association for Vascular Access **9**(2): 80-85.

8. Powls, A. (2018) Peripherally inserted central catheters (PICC Lines) - Neonatology guideline.

9. Yoon, S.-Z., et al. (2005). "Usefulness of the carina as a radiographic landmark for central venous

 catheter placement in paediatric patients." British journal of anaesthesia **95**(4): 514-517.