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Effectiveness of Intracavitary Electrocardiogram guided Peripherally Inserted Central Catheter tip placement in premature infants: A multi-centre pre-post intervention study

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ABSTRACT

This pre-post intervention study was conducted in Neonatal Intensive Care Units in two Chinese hospitals. The objective was to evaluate the effectiveness and safety of intracavitary electrocardiogram (IC-ECG) guided peripherally inserted central catheter (PICC) placement and tip positioning in premature infants. A total of 161 premature infants who required a PICC were enrolled and divided into two groups: Pre-intervention group (n=83) from October 2017 to July 2018, post-intervention IC-ECG group (n=78) from August 2018 to March 2019. Nurses were trained from May 2018 to July 2018. The reposition rate in the IC-ECG group and pre-interventions group was 3.85% and 19.28% respectively (OR 5.970; 95% CI 1.666-21.395; p=0.002). More infants achieved optimal tip position at the first attempt in the IC-ECG group than the pre-intervention group (93.59% versus 73.49%; OR 0.190; 95%CI 0.068-0.531; p=0.001). The overall catheter related complications in the pre-intervention group was 14.46% compared to 3.84% in the IC-ECG group (OR 2.962; 95%CI 1.013-8.661; p=0.040). However, no significant differences were observed between the individual complication leakage, phlebitis and catheter-related blood stream infection. *Conclusions*: IC-ECG guided peripherally inserted central catheter placement and tip positioning technology might decrease reposition rates, achieve more accurate tip positioning at the first attempt and might reduce catheter related complications in premature infants. Further robust RCTs are needed to confirm the effectiveness of IC-ECG guided PICC placement and tip positioning in neonates.

Key word: Electrocardiogram; Tip positioning; Preterm infants; Peripherally inserted central catheter; Chest radiography.

Abbreviations

CRBSI	Catheter-Related Blood Stream Infection
CVC	Central Venous Catheters
IC-ECG	Intracavitary Electrocardiogram
NICU	Neonatal intensive care unit
PICC	Peripherally inserted central catheter

What is Known

- Chest radiography is the gold standard for tip position confirmation of peripherally inserted central catheter placement.
- Studies in adult patients have shown that electrocardiogram guidance in the placement of central venous catheters can be beneficial while evidence in neonates is limited.

What is new

- Intracavitary electrocardiogram guided peripherally inserted central catheter placement might be superior to chest radiography in preterm infants.
- Decreasing the repositioning rates and correct tip position of peripherally inserted central catheters might reduce catheter related complications.

INTRODUCTION

Peripherally inserted central catheter (PICC) is a recommended venous infusion technique which can provide long-term intravenous medication and nutrition to critically ill newborns in neonatal intensive care units (NICU) [1]. Repeated peripheral venipuncture can cause pain and worsen neurodevelopmental outcomes of infants [2]. In addition, it destroys veins now and later in life. Besides, peripheral veins of newborns are fragile and cannot endure the infusion of high concentration fluids [3,4]. Therefore, PICCs are recommended for hospitalized infants in NICU settings.

Generally, PICCs are inserted blindly to a length based on anatomy measurements of estimated distance. The optimal position of the PICC tip is the junction point of the lower third of superior vena cava and right atrium and the tip should not reach the right atrium [5]. Surface landmarks from puncture site to the desired positions is less reliable in neonatal infants than adults and the malposition of PICCs may lead to life-threatening complications [6,7,8]. Studies have shown that infants with PICCs in a central location had significantly lower complication rates than those with the PICC tip in an intermediate or peripheral location [9,10]. Optimal catheter tip position is essential for efficiency and safety of PICC. Currently, chest radiography is a standard method to determine the tip position of PICC as a post-procedural confirmation method. Unfortunately, these catheters are not always placed at the optimal position at the first attempt. Repositioning of the PICC after insertion can cause several complications such as catheter-related bloodstream infection (CRBSI) [11]. It also contributes to delays in care and increases overall procedure time [12]. Reposition followed by further chest radiography also increases the exposure of ionizing radiation in infants and healthcare costs [13].

Real time ultrasound for PICC insertion in the neonatal population has been described as beneficial [14]. A study by Zaghloul and colleagues, including 56 neonates, the agreement coefficient between real time ultrasound and chest radiography in PICC was 0.94 [15]. The use of real-time ultrasound for PICC tip position can also reduce the number of radiography and the overall time of the procedure [11, 16]. Nevertheless, high cost of the equipment and the perceived high degree of training required to perform real time ultrasound during PICC insertion might limit its application and popularization [17].

The use of intracavitary electrocardiogram (IC-ECG) guidance during PICC insertion

procedures to support accurate tip placement is becoming available in NICU settings. The IC-ECG monitor is connected to the infant by three ECG pads and the ECG waves are observed during PICC insertion. A taller or amplified P-wave appears when the catheter is reaching the superior vena cava. When the catheter continues to reach the junction of the superior vena cava and right atrium, the amplitude of the P-wave increases to a peak [18]. A real-time modification of the PICC tip position can be guided by the variation of the amplitude of the P-wave [19]. IC-ECG guided PICC tip positioning technique can help nurses and physicians to identify the PICC tip position in real-time and previous studies in adult patients have proved its effectiveness [20,21]. Although IC-ECG guided PICC tip placement have been utilized in adult patients, its effectiveness in infants has been sparsely demonstrated. Therefore, the aim of this study is to evaluate the effectiveness and safety of IC-ECG guidance in PICC placement and tip position in premature infants.

MATERIALS AND METHODS

Study design

This pre-post intervention study was conducted between October 2017 to March 2019 in the NICUs of two hospitals in China. The study protocol was approved by the Ethics Committee of Hunan Children's Hospital (HCHLL-2018-06). Written consent forms were collected from the parents and they were informed that their decision to refuse or withdraw from the study would not impact on the care of their infant.

The reporting guideline 'template for intervention description and replication' (TIDieR) has been used to describe the intervention in this study [22].

Setting

This study was conducted in two tertiary hospitals. The first hospital was Hunan Children's Hospital, a tertiary children's hospital in Hunan Province, China. The NICU division included five NICUs; Two level-III NICUs for preterm infants (60 beds), two level-II NICUs for term infants with 70 beds and one NICU for surgical infants with 50 beds. The study was performed at the level-III NICU for preterm infants and term infants. The second hospital was Xiangtan Central Hospital located in Hunan Province, a tertiary hospital with a paediatric department. The NICU in this hospital had 40 beds.

Sample size calculation

As reported in previous research [23], the optimal target rate of PICC with chest radiography was 62.5%, and with the aid of IC-ECG, the optimal target rate was predictable to be 88%. Assuming that α = 0.05, β = 0.1, according to the formula:$n = (p_1q_1 + p_2q_2)\left(Z_\alpha + Z_\beta\right)^2 / (p_1 - p_2)^2$, infants included in each group should be 70. We estimated a drop-out rate of 10%, resulting in a total sample size of 156 infants to be included. Finally, we included 161 preterm infants in the study.

Patients

We included 161 preterm infants who required PICC placement (Fig 1). Infants requiring a PICC from October 2017 to July 2018 were included into the standard group (n=83) and infants from August 2018 to March 2019 were allocated into the IC-ECG group (n=78). The IC-ECG group received IC-ECG guided PICC insertion, the standard group received the routine PICC placement procedure. Participants were eligible for this study if they were: infants with gestational age <37 weeks; normal sinus rhythm with visible P-wave on the ECG monitor and without heart pacemaker; parents' approval. Exclusion criteria were: congenital heart disease, coagulation dysfunction or thoracic deformity.

IC-ECG guided PICC placement and standard procedure

In both NICUs, PICC placements were performed by 12 qualified nurses following the 2006 guidelines of Infusion Nursing Standards of Practice [5]. These guidelines were used in the PICC training prior to the implementation of using IC-ECG guided PICC placement. Seven nurses from the NICU III in Hunan Children's Hospital and five nurses from the NICU in Xiangtan Central Hospital received the training and were qualified for PICC placement in infants. The nurses at the NICU-III in Hunan Children's Hospital insert around 200 PICCs annually in term and preterm infants; nurses in Xiangtan Central Hospital insert around 100 PICCs annually.

The PICC lines utilized in the NICUs were 1.9Fr PICC catheters with stylet (Medical components, 1499 Delp Drive, Harleysville, PA 19438 USA). The IC-ECG monitor (Coman C100B Multi-functional ECG monitor, Shenzhen Coman medical Instruments Co, Ltd, China) with three-lead were used to monitor the P-wave in lead II and the mode of the monitor was

switched to intra-atrial ECG mode.

Every PICC placement was performed by two nurses. Infants were kept in supine position and sucrose, pacifiers, and facilitating tucking were provided to comfort the infants. Cotton with 75% ethanol was utilized to clean the skin, then three electrode pads were attached to skin below the left subclavian, the right subclavian and the lower left abdomen respectively. Ultrasound was utilized to confirm the optimal puncture sites. The insertion of PICC was guided by the changes of the P-wave when the catheter entered the superior vena cava. After the amplitude of the P-wave showed an increased peak, the PICC was pulled back about 0.5 cm and fixed. The catheter was flushed with normal saline and 5U/ml heparin according to the guideline [5]. The PICC tip position was confirmed by chest radiography. If reposition of the PICC tip position was indicated by chest radiography result, an additional chest radiography was performed to confirm adequate adjustment.

The standard procedure of PICC insertion was similar as described above without the procedure of using the IC-ECG monitor. The nurses measured an estimated length of the PICC by anatomic length and inserted the catheter blindly. The confirmation of the tip position and reposition was similar as described in the IC-ECG procedure.

Outcome measures

Infants characteristics were collected and compared between both groups. Characteristics were: gender, gestational age, birth weight, days of age and weight at catheterization. The aim of this study was to evaluate the effectiveness and safety of IC-ECG guided PICC placement and tip position in premature infants. The outcome measures to test the effectiveness were: repositioning rate, optimal tip location and optimal tip location. Optimal position of the PICC tip was defined as in the lower third of the superior vena cava or at the cavo-atrial junction [21,24]. The outcome measures to evaluate the safety of PICC placement were defined as catheter-related complications: leakage at the insertion site, phlebitis and catheter-related blood stream infection (CRBSI). Leakage at the insertion site was observed by the nurses and was documented when fluid leakage was seen under the transparent dressing. Although no universal definition of phlebitis is available [25], we defined phlebitis in our population as erythema at access site. Catheter-related blood stream infection was defined as a primary blood stream infection in an infant with a PICC within a 48-hour period prior to the onset of the blood stream

infection and the infection was not related to another infection [26,27].

Statistical analysis

Data analysis was performed with SPSS version 21.0 software (Armonk, New York: IBM Corp), mean and standard deviation were applied for descriptive statistics and percentage for categorical variables. The independent Student t test was used for continuous variables and the chi-square test for categorical variables. A *p* value below 0.05 was considered as statistically significant.

RESULTS

A total of 161 infants with a gestational age between 28 to 37 weeks who required PICC insertion were enrolled in this study and all the PICCs were placed in upper extremity. In the pre-intervention phase, 83 infants were included in the standard group and 78 infants were included in the IC-ECG group (Fig 1).

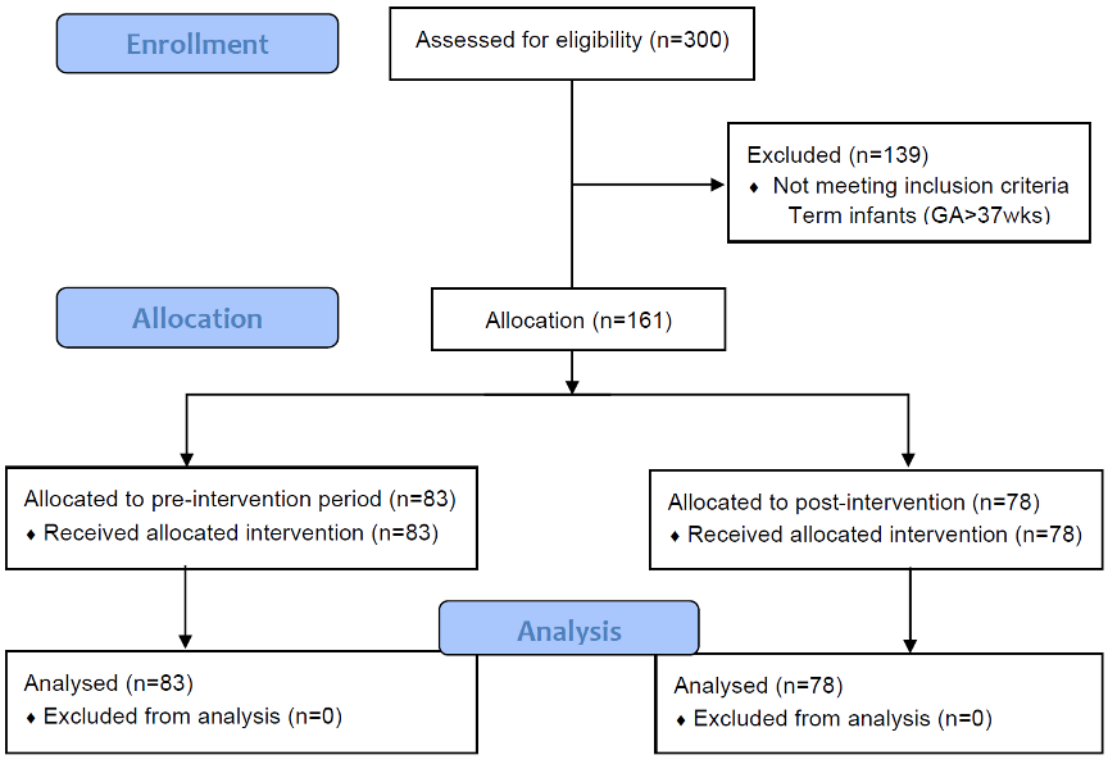

Figure 1. Study Flowchart

The infants in both groups did not differ for gender, gestational age, birthweight, days of age and weight at catheterization (Table 1).

Table 1 Baseline characteristics of Standard group and IC-ECG group

Baseline characteristics	Standard group （n=83）	IC-ECG group (n=78)	*p*
Gender, male, n (%)	43 (51.81)	42 (53.85)	0.796
Gestational age, (wk), mean (SD)	32.36 (2.78)	32.17 (2.63)	0.649
Birth weight (g), mean (SD)	1508.13 (279.31)	1520.00(377.38)	0.820
Days of age, mean (SD)	13.19 (8.80)	15.21 (7.52)	0.122
Weight at catheterization (g), mean (SD)	1571.63 (266.16)	1657.44 (307.22)	0.060

g, gram; IC-ECG, intracavitary electrocardiogram; SD, standard deviation; wk, weeks.

Infants in the IC-ECG group needed less repositioning of the PICC after initial placement compared to infants in the standard group (Table 2). In the standard group, 16 infants required repositioning and additional chest radiography, while only three infants in the IC-ECG group required repositioning (OR 5.970; 95%CI 1.666-21.395; p=0.002). Nevertheless, it was observed that variation of the P-wave on the IC-ECG monitor was detected in all cases, but ambiguous P-wave changes were detected in three infants who needed repositioning. These vague P-wave signals could explain the incorrect PICC tip position in the IC-ECG group. Infants in the IC-ECG group had more accurate PICC positions at the first attempt compared to the standard group; 93.59% vs 73.49%, p=0.001 (Table 2).

Table 2 Tip position comparison of standard group and IC-ECG group

Tip position	Standard group (n=83)	IC-ECG group (n=78)	OR (95% CI)	*p*
Repositioning rate (n, %)	16 (19.28)	3 (3.85)	5.970 (1.666-21.395)	0.002
Optimal tip location at first attempt (n, %)	61(73.49)	73 (93.59)	0.190 (0.068-0.531)	0.001
Sub-optimal tip location at first attempt (n, %)	6 (7.23)	2 (2.56)	2.961 (0.579-15.134)	0.318

CI, confidence interval; IC-ECG, intracavitary electrocardiogram; OR, odds ratio.

Of all infants, 19 infants (11.8%) developed catheter related complications with 14 in the standard group and five in the IC-ECG group (p=0.040). Table 3 presents the catheter related complications. The three complications, leakage of the PICC, phlebitis, and CRBSI did not show any differences.

Table 3 comparison of catheter related complications between Standard group and IC-ECG group

Catheter related complications	Standard group (n=83)	IC-ECG group (n=78)	OR (95% CI)	p
Leakage (n, %)	4 (4.82)	2 (2.56)	1.924 (0.342-10.813)	0.735
Phlebitis (n, %)	7 (10.84)	2 (2.56)	1.924 (0.342-10.813)	0.202
CRBSI (n, %)	3 (3.61)	1 (1.28)	2.888 (0.294-28.363)	0.657
Total (n, %)	14 (14.46)	5 (3.84)	2.962 (1.013-8.661)	0.040

CI, confidence interval; CRBSI: catheter-related blood stream infection; IC-ECG, intracavitary electrocardiogram; OR, odds ratio.

DISCUSSION

In our study, we found that IC-ECG guided PICC placement reduced the repositioning rate and achieved more optimal tip locations at the first attempt. Although IC-ECG technology can achieve higher accurate PICC positions at insertion, not all PICC tip positions were successfully placed in the optimal position at the first attempt. However, limitations still exist when using an IC-ECG monitor such as functional errors or infants' crying might contribute to the invisible P-waves during the process of PICC insertion.

In the meta-analysis of Liu and colleagues including 827 adult patients in five studies without IC-ECG, PICC tip positioning accuracy was 77.1%, while the tip positioning accuracy

245 in the IC-ECG group was 89.7% [28]. Although this meta-analysis included only adult patients,
246 the results of our study showed similar accuracy rates. The use of IC-ECG monitors to verify
247 PICC tip placement has been used in clinical practice for some years. A vascular access team
248 in the UK performed an audit over a 5-year period and identified an increase of accurate optimal
249 PICC tip placement of 85% in 2011 to 98% in 2015 [29]. Besides, this team also documented
250 that the use of IC-ECG guidance technology resulted in significant cost-savings due to the
251 reduced costs of post-procedural chest X-ray for PICC tip confirmation and a reduction in
252 procedure time [29]. Specifically, in infants, the study by Zhou et al [23] demonstrated that IC-
253 ECG guided PICC placement in 49 premature infants gained higher success rate of correct
254 PICC tip position (94%) compared to 200 premature infants with the traditional PICC
255 placement (63%). These results are comparable with our study. We demonstrated an optimal tip
256 location at first attempt of 94% in the IC-ECG group compared to 73% in the standard group.
257 The results of both studies might indicate that IC-ECG monitoring could be encouraged for
258 guiding PICC insertion and placement.

259 Success rates of PICC insertion and placement might not only rely on IC-ECG guidance.
260 The experiences of a vascular nursing team are important and might contribute to the success
261 of placing a PICC. In our study, we had a designated nursing team specifically trained for PICC
262 placement which could have benefit the safety of the procedures in terms of complication rates.
263 Studies with a special designated vascular access team in the NICU have demonstrated a
264 decrease in central line-associated bloodstream infections in infants [30]. A systematic review
265 of seven studies, including 136 to 414 infants, identified a decrease in catheter-associated
266 bloodstream infection between 1.4 to 10.7 per 1000 catheter-days after initiating a designated

vascular access team [30]. Although the authors of this review state that implementing a vascular access team is a promising intervention, the level of evidence of the included studies was low indicating that more robust studies are needed to support designated and well-trained nursing teams for PICC procedures. The implementation of the IC-ECG guided technique for PICC placement enables nurses to support and adjust the tip positions in real-time by monitoring the variation of P-wave to achieve the optimal tip location. In the process of insertion, if a certain length of the catheter has been inserted without the appearance of a characteristic P-wave, it is suggested that catheter adjustment should be performed immediately [31]. Thus, specific training for vascular access team is suggested to increase the competencies and ultimately increase the success rates of PICC placements [32].

In our study, safety of the PICC placement was related to catheter related complications and these were compared between the standard group and IC-ECG group. Our results documented that the complication rates of phlebitis, leakage and CRBSI were relatively low. A meta-analysis showed that the rate of phlebitis in the upper extremity for neonates was 3.53% (65/1839) and the rate of catheter-related infections was 7.23% (133/1839) [33]. Unfortunately, we did not collect the data of the PICC position and, therefore, we were unable to correlate these with the identified complication rates.

Immunity of premature infants is low, and this vulnerable population is prone to infection. Relocating PICC tip positions might be a risk factor of catheter-related infections and contribute to CRBSI of infants. Other risk factors have been identified by Jumani and colleagues [34]. In their large cohort of children, 2574 PICC placements in 1807 children, the authors identified when a PICC is not centrally located that this would contribute to a modifiable risk factor for

289 complications and possibly requiring PICC removal. Using the IC-ECG technique for PICC
290 insertion and placement might contribute to the safety of care in premature infants. Chest
291 radiography remains still the gold standard till compelling evidence to change this standard
292 becomes available to use only IC-ECG guided PICC placement in neonates. However, the
293 healthcare team should be aware that radiation caused by chest radiography may pose potential
294 harm for infants. It is reported that radiation may lead to cardiac disease, which may manifest
295 years after radiation exposure, and this is associated with higher morbidity and mortality [35].
296 Yu's retrospective multicentre study [21] and Rossetti's multicentre study [36] showed that
297 matching rates between IC-ECG and the chest radiography method to confirm PICC or CVC
298 tip placement was 93.7% and 95.8% respectively. While IC-ECG technology has demonstrated
299 advantages such as reducing medical cost, lower incidence of complications, less repositioning,
300 more robust evidence is needed to confirm this new technique in infants.
301 Some study limitations need to be addressed. Although the nurses were trained and
302 qualified for PICC placements, their experiences of PICC placements differed between both
303 hospitals because of the number of PICC placements. We did not include organizational and
304 workforce factors such as the number of PICC placement experiences of nurses. The number
305 of participants was relatively small, and we did not initiate a randomized controlled trial design
306 limiting the level of robustness of our study generalisability. Therefore, our study might provide
307 limited strong evidence for the general adoption and application of IC-ECG guidance during
308 PICC placements in infants. This is, for example, reflected in the safety outcome measures
309 where total numbers where small, limiting the interpretation of statistical significance. Besides,
310 we only evaluated the optimal tip locations and catheter related complications; the overall

procedure time and cost were not evaluated and should be included in future studies.

Conclusion

The results of our study suggest that IC-ECG guided PICC placement might contribute to lower PICC repositioning rates, higher rates of optimal tip locations at the first attempt, and reduced rate of catheter related complications. Using an IC-ECG monitor is a promising technique for PICC placement and might be more effective than chest radiography for PICC tip placement confirmation. Further studies are needed to confirm these assumptions and provide more robust evidence for IC-ECG guided PICC insertion in infants.

Author Contributions

ZyL and LhZ designed the study and study protocol. ZyL, LhZ, JML provided ongoing support to the study team. PS, ZyL and LlZ contributed to the data collection. AqX and JS performed the data analysis and interpretation. AqX, JS, JML drafted the first manuscript. All authors provided comments to manuscript drafts and all authors approved the final manuscript version.

Compliance with ethical standards

All procedures performed in the studies were in accordance with the ethical standards of Ethics Committee of Hunan Children's Hospital, Xiangtan Central Hospital, and the Declaration of Helsinki.

Conflicts of Interest

All authors declare no competing interest and no financial conflicts.

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Ethical approval

The protocol was approved by the Ethics Committee of Hunan Children's Hospital (HCHLL-2018-06). Parents were informed that their decision to refuse or withdraw from the study would not impact on the care of their infant.

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Informed consent

Written informed consent was obtained from all parents included in the study.

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