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

3

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36 **ABSTRACT**

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

55

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

58 **Abbreviations**

59 CRBSI Catheter-Related Blood Stream Infection

60 CVC Central Venous Catheters

61 IC-ECG Intracavitary Electrocardiogram

62 NICU Neonatal intensive care unit

63 PICC Peripherally inserted central catheter

64

65 **What is Known**

66 • Chest radiography is the gold standard for tip position confirmation of peripherally inserted  
67 central catheter placement.

68 • Studies in adult patients have shown that electrocardiogram guidance in the placement of  
69 central venous catheters can be beneficial while evidence in neonates is limited.

70 **What is new**

71 • Intracavitary electrocardiogram guided peripherally inserted central catheter placement  
72 might be superior to chest radiography in preterm infants.

73 • Decreasing the repositioning rates and correct tip position of peripherally inserted central  
74 catheters might reduce catheter related complications.

75 **INTRODUCTION**

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

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

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

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

105 procedures to support accurate tip placement is becoming available in NICU settings. The IC-  
106 ECG monitor is connected to the infant by three ECG pads and the ECG waves are observed  
107 during PICC insertion. A taller or amplified P-wave appears when the catheter is reaching the  
108 superior vena cava. When the catheter continues to reach the junction of the superior vena cava  
109 and right atrium, the amplitude of the P-wave increases to a peak [18]. A real-time modification  
110 of the PICC tip position can be guided by the variation of the amplitude of the P-wave [19]. IC-  
111 ECG guided PICC tip positioning technique can help nurses and physicians to identify the PICC  
112 tip position in real-time and previous studies in adult patients have proved its effectiveness  
113 [20,21]. Although IC-ECG guided PICC tip placement have been utilized in adult patients, its  
114 effectiveness in infants has been sparsely demonstrated. Therefore, the aim of this study is to  
115 evaluate the effectiveness and safety of IC-ECG guidance in PICC placement and tip position  
116 in premature infants.

117

## 118 **MATERIALS AND METHODS**

### 119 **Study design**

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

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

### 127 **Setting**

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

135 **Sample size calculation**

136 As reported in previous research [23], the optimal target rate of PICC with chest radiography  
137 was 62.5%, and with the aid of IC-ECG, the optimal target rate was predictable to be 88%.

138 Assuming that  $\alpha = 0.05$ ,  $\beta = 0.1$ , according to the formula:  $n = (p_1q_1 + p_2q_2)(Z_\alpha + Z_\beta)^2 /$   
139  $(p_1 - p_2)^2$ , infants included in each group should be 70. We estimated a drop-out rate of 10%,  
140 resulting in a total sample size of 156 infants to be included. Finally, we included 161 preterm  
141 infants in the study.

142 **Patients**

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

151 **IC-ECG guided PICC placement and standard procedure**

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

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



164 switched to intra-atrial ECG mode.

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

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

#### 180 **Outcome measures**

181 Infants characteristics were collected and compared between both groups. Characteristics were:  
182 gender, gestational age, birth weight, days of age and weight at catheterization. The aim of this  
183 study was to evaluate the effectiveness and safety of IC-ECG guided PICC placement and tip  
184 position in premature infants. The outcome measures to test the effectiveness were:  
185 repositioning rate, optimal tip location and optimal tip location. Optimal position of the PICC  
186 tip was defined as in the lower third of the superior vena cava or at the cavo-atrial junction  
187 [21,24]. The outcome measures to evaluate the safety of PICC placement were defined as  
188 catheter-related complications: leakage at the insertion site, phlebitis and catheter-related blood  
189 stream infection (CRBSI). Leakage at the insertion site was observed by the nurses and was  
190 documented when fluid leakage was seen under the transparent dressing. Although no universal  
191 definition of phlebitis is available [25], we defined phlebitis in our population as erythema at  
192 access site. Catheter-related blood stream infection was defined as a primary blood stream  
193 infection in an infant with a PICC within a 48-hour period prior to the onset of the blood stream

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

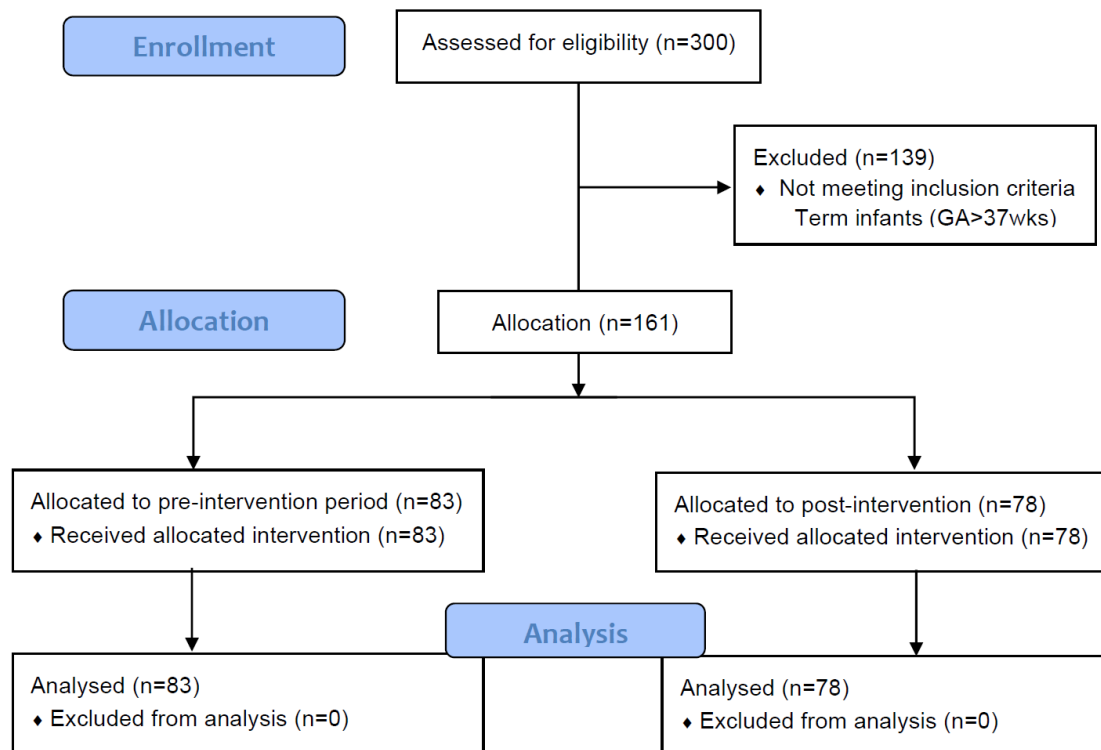
### 195 **Statistical analysis**

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

201

### 202 **RESULTS**

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



207

208 **Figure 1.** Study Flowchart

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

211

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

| Baseline characteristics                 | Standard group<br>(n=83) | IC-ECG group<br>(n=78) | <i>p</i> |
|--|--------------------------|------------------------|----------|
| 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    |

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

214

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

224

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

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

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

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

231

232 **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)          | <i>p</i> |
|--------------------------------|-----------------------|---------------------|----------------------|----------|
| 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    |

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

235

236 **DISCUSSION**

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

243 In the meta-analysis of Liu and colleagues including 827 adult patients in five studies  
 244 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

267 vascular access team [30]. Although the authors of this review state that implementing a  
268 vascular access team is a promising intervention, the level of evidence of the included studies  
269 was low indicating that more robust studies are needed to support designated and well-trained  
270 nursing teams for PICC procedures. The implementation of the IC-ECG guided technique for  
271 PICC placement enables nurses to support and adjust the tip positions in real-time by  
272 monitoring the variation of P-wave to achieve the optimal tip location. In the process of  
273 insertion, if a certain length of the catheter has been inserted without the appearance of a  
274 characteristic P-wave, it is suggested that catheter adjustment should be performed immediately  
275 [31]. Thus, specific training for vascular access team is suggested to increase the competencies  
276 and ultimately increase the success rates of PICC placements [32].

277 In our study, safety of the PICC placement was related to catheter related complications  
278 and these were compared between the standard group and IC-ECG group. Our results  
279 documented that the complication rates of phlebitis, leakage and CRBSI were relatively low. A  
280 meta-analysis showed that the rate of phlebitis in the upper extremity for neonates was 3.53%  
281 (65/1839) and the rate of catheter-related infections was 7.23% (133/1839) [33]. Unfortunately,  
282 we did not collect the data of the PICC position and, therefore, we were unable to correlate  
283 these with the identified complication rates.

284 Immunity of premature infants is low, and this vulnerable population is prone to infection.  
285 Relocating PICC tip positions might be a risk factor of catheter-related infections and contribute  
286 to CRBSI of infants. Other risk factors have been identified by Jumani and colleagues [34]. In  
287 their large cohort of children, 2574 PICC placements in 1807 children, the authors identified  
288 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 were small, limiting the interpretation of statistical significance. Besides,  
310 we only evaluated the optimal tip locations and catheter related complications; the overall

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

### 312 **Conclusion**

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

319

### 320 **Author Contributions**

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

325

### 326 **Compliance with ethical standards**

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

330

### 331 **Conflicts of Interest**

332 All authors declare no competing interest and no financial conflicts.



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338

339 **Ethical approval**

340 The protocol was approved by the Ethics Committee of Hunan Children's Hospital (HCHLL-  
341 2018-06). Parents were informed that their decision to refuse or withdraw from the study  
342 would not impact on the care of their infant.

343

344 **Acknowledgement**

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347

348 **Informed consent**

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

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