Umbilically and Peripherally Inserted Thin Central Venous Catheters Have Similar Risks of Complications in Very Low Birth Weight Infants

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2 venous catheters have similar risks of
3 complications in very low birth weight infants

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16

17 Short title: Catheter complications in very low birth weight infants

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21

Abstract.

In order to compare the complications associated with thin (1-2F) umbilical vein catheters (tUVC) and peripherally inserted central catheters (PICC) in very low birth weight (VLBW) infants, the frequencies and causes of the non-elective removal of first tUVCs and PICCs were evaluated in 195 VLBW infants born in one hospital. Data were collected from patient records. Risk factors for catheter complications were analysed using logistic regression analysis. Altogether, 92 (47%) infants had tUVCs, and 103 (53%) PICCs. In total, 78 (40%) infants underwent the non-elective removal of their first catheters, most commonly due to suspected infection (n=42) or catheter dislocation (n=30). Infants with complications had lower birth weights and gestational ages than those without. The frequencies and causes of the non-elective catheter removal were similar in the tUVC and PICC groups. True catheter infection was diagnosed in 31 infants. The number of infections/1,000 catheter days was higher in the tUVC than in the PICC group. In a multivariable analysis, gestational age was found to be associated with catheter infection, but catheter type was not.

Conclusion: The odds of catheter complications seem to decrease with increasing gestational age, but no clear association with thin catheter type was found.

Key words: catheter complication, catheter infection, peripherally inserted central catheter, thin umbilical catheter, very low birth weight infant

Introduction

Very low birth weight (VLBW) infants require time before beginning enteral feeding, and parenteral nutrition may be required for many weeks. Central venous catheters (CVCs) ensure the administration of sufficient parenteral nutrition, fluids and medication. Peripherally inserted central catheters (PICCs) are thin and can be inserted and removed without anesthesia, but the risk of complications, associated with prolonged hospitalisation, morbidity and even death (1), exists.

53 By using the umbilical vein as a catheter route, painful skin penetration, which
 54 may be associated with an increased risk of infection, can be avoided. The increased risk of
 55 complications, especially thrombosis, associated with traditional (3,5-5 F) umbilical venous
 56 catheters inhibits their long-term use (2).

57

58 Several studies have found no differences between PICCs and traditional umbilical venous
 59 catheters (UVCs) in terms of general complication (3, 4) or catheter infection rates (5, 6), but
 60 one study found highest CVC-associated infection rates with umbilical catheters (7).

61 Peripherally inserted central catheters and thin (2F) umbilically inserted silicone central
 62 venous catheters (tUVC) seem to pose an equal risk of thrombosis, catheter-related sepsis
 63 and obstruction (8). More information is needed regarding their use in VLBW infants.

64

65 Here, the aim was to investigate 1.) the frequency and type of complications in the first thin
 66 CVCs, 2.) the differences in catheter complications between tUVCs and PICCs and 3.)
 67 the predictors of catheter-related complications, especially catheter infections in VLBW
 68 infants.

69

70 **Subjects and methods**

71

72 The population consisted of 232 VLBW infants (birth weight 1,500g or below) who were born
 73 in Tampere University Hospital, during the years 2011-2016 and had received a tUVC or
 74 a PICC as the first CVC. Infants who were transferred to another hospital (N=19) or died
 75 (N=18) before removal of the first CVC were excluded. To enable a comparison between
 76 tUVCs and PICCs, only the first CVC episode was analysed. The final population included
 77 195 infants (Figure 1). No significant differences were detected between included and
 78 excluded infants in terms of birth weight or gestational age (data not shown). The study was
 79 approved by the ethical committee of Pirkanmaa Hospital District (registration ID=R19095R).

80

81 Information was collected from patient records (Table 1). Chorioamnionitis was considered to
 82 be an obstetric clinical diagnosis, as defined previously (9). Infants with a birth weight below

83 the 10th percentile, adjusted for gestational age, were considered small for gestational age
84 (SGA) (10, 11). A diagnosis of necrotising enterocolitis (NEC) was made according to the
85 Bell criteria (at least stage 2) or intraoperative biopsy (12).

86

87 A PICC or tUVC was inserted if the expected duration of parenteral nutrition was at
88 least one week. It was usually removed when enteral feeding of 130ml/kg/day was reached.
89 After removal, the catheter tip was sent for bacterial culture. During the study period, tUVC
90 was preferred as the first CVC in VLBW infants over PICC. The UVC was inserted as
91 described by Haumont (8) and covered with gauze and a transparent medical dressing. The
92 PICC was usually inserted into a cubital vein using an introducer and then covered with a
93 transparent medical dressing. The catheter tip position was verified by X-rays with contrast
94 media, with the optimal position being extracardial in the central veins.

95

96 Aseptic principles were followed in the handling of the catheters. Checklists for the insertion
97 and maintenance of the catheters were implemented during 2015, and since then, the
98 practice has been to remove or change thin CVCs after 14 days' dwell time if possible. A
99 multidisciplinary group supervised the hygienic procedures on the ward.

100

101 Our primary outcome measure was catheter complication, defined as non-elective catheter
102 removal for a catheter-related reason more than 24 hours after insertion. Complications were
103 classified as follows: suspected infection, dislocation and other complications
104 (disconnected/blocked/broken).

105

106 In the subgroup analysis of catheter infections, we used two time periods: 1) within one day
107 before and one day after catheter removal and 2) within three days before and three days
108 after catheter removal. The diagnostic criteria for true catheter infection included a positive
109 blood culture without any other focus, as well as the symptoms and signs of infection, such
110 as temperature instability, hypotension, apnea, increased need for oxygen and/or ventilatory
111 support, heart rate abnormalities, feeding intolerance, lethargy, irritability, skin lesions and at
112 least one of the following laboratory parameters: white blood cell count <5 or $>30 \times$

113 10^9 cells/L, immature to total neutrophil ratio >0.2, absolute neutrophil count <1000/ μ L,
 114 platelet count <100 x 10^9 /L, CRP >15 mg/L, glucose intolerance or hypoglycemia, acidosis
 115 (modified from (13, 14)).

116

117 *Statistical analysis*

118 Group comparisons with categorical variables were performed using crosstabulation and the
 119 Chi-square or Fisher's exact test, and those with continuous variables were performed using
 120 a Mann-Whitney U-test. Differences between catheter types in terms of the frequencies of
 121 complications and true catheter infections were also analysed per 1,000 catheter days using
 122 the OpenEpi program's Mid-p procedure.

123

124 Risk factors were analysed using univariable and multivariable logistic regression analysis
 125 separately for 1) any catheter complication and 2) true catheter infection diagnosed within
 126 three days before or after catheter removal. The independent variables were gestational age
 127 at birth (weeks), SGA (no/yes), gender (female/male), mode of delivery (vaginal/cesarean
 128 section), need for mechanical ventilation (no/yes) and central venous catheter type
 129 (tUVC/PICC). Gestational age and ventilator therapy were included in the models based on
 130 the results of univariable analyses, SGA to take into account birth weight, and gender and
 131 mode of delivery as known factors affecting neonatal outcomes.

132

133 P-values <0.05 (two-sided) were considered to be statistically significant. Statistical analyses
 134 were performed using SPSS (Versions 24 and 25).

135

136 **Results**

137

138 *Catheter complications*

139 Altogether, 92 (47%) infants had a tUVC and 103 (53%) infants a PICC. In total 78 (40%)
 140 infants underwent non-elective removal of their first catheter. Of these, 42 (54%) were
 141 removed for suspected infection, 30 (38%) for dislocation and six (7.8%) for other reasons

142 (three disconnected, two broken and one obstruction) (Figure 1). The median catheter dwell
 143 time at non-elective removal was 10 days.

144

145 Clinical characteristics of the infants are presented in Table 1. Infants who had catheter
 146 complications in their first catheter had lower birth weights, were born more premature and
 147 needed ventilator therapy more commonly and for longer periods.

148

149 *Comparison between catheter types*

150 The comparisons between infants with tUVCs and those with PICCs are presented in Table
 151 2. Umbilical catheters were inserted at an earlier age than PICCs (md(range) 0 (0–5) vs 2 (0–
 152 32) days, $p < 0.001$. The most common reason for the non-elective removal of tUVCs was
 153 suspected infection and dislocation for PICCs. No significant difference was found in the total
 154 catheter complication rate between infants with tUVCs and those with a PICC. True catheter
 155 infection within ± 3 days from catheter removal was more common in the tUVC group than in
 156 the PICC group, but the groups did not differ in terms of the ± 1 day criteria. The occurrence
 157 of NEC was similar between the groups (tUVC 12 (13.0%) vs PICC 14 (13.6%), $p = 0.910$).

158

159 Ten infants died during their hospital stays after the removal of the first catheter. There were
 160 more deaths in the tUVC group than the PICC group (8(8.7%) vs. 2(1.9%), $p = 0.033$). In two
 161 tUVC cases, the cause of death was catheter sepsis. Eight deaths did not have catheter-
 162 related causes and occurred 4–44 days after the removal of the first catheter.

163

164 *Risk factors for catheter complications and catheter infections*

165 The results of risk factor analyses of catheter complications generally are presented in Table
 166 3. Low gestational age and ventilator therapy were associated to catheter complication in the
 167 univariable analysis. In the multivariable logistic regression analysis, gestational age
 168 was marginally significantly associated with catheter complications generally, with an OR
 169 (95%CI) of 0.822 (0.675–1.000), $p = 0.05$, but ventilator therapy was not.

170

171 Altogether, 21 (10.8%, 8.4/1000 catheter days) infants had true catheter infection (positive
172 blood culture combined with symptoms) within +/-1 day of catheter removal, and 31 (15.9%,
173 12.3/1000 catheter days) infants had such within +/- 3 days of catheter removal. Among the
174 latter, 26 catheters were removed due to suspected infection, one due to catheter
175 obstruction, and four electively. In these five cases, signs and symptoms of
176 infection developed within three days after catheter removal.

177

178 In the univariable analysis, lower gestational age and ventilator therapy were associated with
179 true catheter infection within 3 days before or after catheter removal, but in the multivariable
180 logistic regression analysis only gestational age remained significant risk factor. No
181 association was found between catheter infection and CVC type. (Table 3)

182

183 The most common pathogen in both blood cultures and catheter tip cultures was coagulase-
184 negative staphylococcus (*CoNS*). Tip culture findings were available from 139 (71.3%)
185 catheters. Of these, 62 (44.6%) revealed pathogen growth, including 30 (35%) of the
186 electively removed catheters and seven that were removed due to a dislocation. The tip
187 culture was positive in 19 of 31 (61.3%) catheters in the true catheter infection group, and in
188 13 (41.9%), the culture revealed the same bacteria in both the blood and catheter tip.

189

190 **Discussion**

191

192 In this study of VLBW infants, non-elective removals of thin umbilical CVCs and the first
193 peripherally inserted CVCs were common. Nearly half of the removals were due to
194 suspected infection. We did not find significant differences between total complication rates
195 with the use of either tUVCs or PICCs, but non-elective removals due to suspected
196 infection were more common in the tUVC group. Two infants with tUVCs died due to catheter
197 infection. Also, the rate of infections/1,000 catheter days was higher in the tUVC group than
198 the PICC group. However, in the multivariable logistic regression analysis, the only
199 statistically significant risk factor for true catheter infection was low gestational age.

200

201 In the earlier studies non-elective PICC removal rates in neonates (3, 15-17) or infants (1)
202 have varied from 9.97% to 37.2%. In our study, a high percentage (40%) of the first thin
203 CVCs (PICC or tUVC) were removed non-electively. Differences in patient populations and
204 the definitions of complications mostly account for differences between studies. We did not
205 find any significant differences between the overall complication rates of the tUVC or PICC.
206 Previous studies have investigated mainly traditional, uncovered UVC catheters and had
207 different study design so they are not comparable with our study. (4, 7,9,11) To our
208 knowledge, this study is one of the few focusing on premature VLBW infants and the use of
209 tUVCs,

210

211 As in prior studies (1, 15, 17), infants with any catheter complications had lower birth
212 weights and gestational ages than those without complications. They were also more
213 commonly and lengthily exposed to invasive treatments, including ventilator therapy and
214 parenteral nutrition. We focused on the complications regarding the first thin CVCs, and no
215 strict conclusions can be drawn regarding their role in the development of later problems,
216 such as NEC.

217

218 In our population infants with tUVC were lighter and more premature at birth than infants with
219 PICC, which might contribute to the differences in infections and death rates. The greater
220 percentage of deaths in the tUVC group was probably not associated with the use of tUVCs.
221 Multivariable logistic regression analysis did not reveal any association between catheter
222 type and the risk of either any catheter complication or catheter infection. Thin UVC has
223 some benefits compared to PICC, because it can be inserted pain free, without penetrating
224 the skin of a fragile infant. When tUVC is used as the first CVC, the peripheral veins remain
225 intact for later use, which is beneficial, especially when the need for prolonged parenteral
226 nutrition is likely.

227

228 Our definitions of catheter related sepsis were based on positive blood cultures and
229 symptoms and laboratory findings compatible with infection within one or three days before
230 and after catheter removal. The removal of CVCs has been suggested to induce bacteremia,

231 occurring within 72 hours after catheter removal, even in 23% of the sepsis cases (18). We
232 included this wider timeframe to ensure that no catheter related infections would be
233 missed. The shorter timeframe is in accordance with Center for Disease Control and
234 Prevention criteria (19).

235

236 Previous studies have reported sepsis rates of 1.66–18.1/1,000 catheter days (5-7, 20, 21).
237 Our infection rates were within this range. The various hygienic practices of the units, ward
238 patient loads and patient case mixes help explain the differences between studies. According
239 to our logistic regression analysis, the most important risk factor for catheter infections
240 was low gestational age, as reported previously (15, 20). An increased need for invasive
241 treatments, fragile skin barriers and immature immune systems contribute to an increased
242 risk for infections (22) in very low gestational age infants.

243

244 In line with previous studies, CONS was the most common pathogen found in the blood (2, 6,
245 20, 21, 23) and catheter tip cultures (15). Asymptomatic bacterial contamination of the
246 catheters were common (24). The use of catheter tip cultures as diagnostic criteria for
247 catheter related sepsis is challenging. The infant may have received several antibiotic doses,
248 sometimes to the CVC, before the removal of the catheter, which may bias the culture
249 results.

250

251 The limitations of this study were its retrospective design and relatively small sample size.
252 However, our results add knowledge about CVC complications in VLBW infants. The
253 catheter-related sepsis classification we used was clinically applicable. Because all infants
254 were treated in one unit, we had access to all clinical details in the patient records. Treatment
255 practices did not differ markedly between patients.

256

257 **Conclusion**

258

259 Gestational age was associated with both central venous catheter complications and
260 infections in VLBW infants. No clear association was found between central venous catheter

261 type and catheter complications. Our data suggest that neither tUVCs nor PICCs seem to be
 262 superior regarding complication risk.

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Figures

Figure 1

Study population, CVC=central venous catheter, PICC=peripheral inserted central catheter, tUVC= thin (1-2F) umbilically inserted central venous catheter. Complication was defined as a non-elective removal of the catheter

Supplementary Files

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