ORIGINAL ARTICLE

Early Elective Replacement of Umbilical Venous Catheter with Peripherally Inserted Central Catheter to Reduce Central Line-Associated Blood Stream Infections in Premature Infants: A Randomized Trial

Suparanan Phumyeesoon, MD[1], Pichaya Thanomsingh, MD[1]

[1] Department of Pediatrics, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand

Background: Central-line umbilical venous catheter (UVC) insertion at birth and replacement later with a peripherally inserted central catheter (PICC) is often required in VLBW infants for medical and nutritional support. A serious complication of central line is associated with bloodstream infections (CLABSIs). There is no consistent evidence about the effect of dwell time of UVC or the time of PICC replacement on the risk of CLABSI in VLBW infants.

Objective: To compare the CLABSI rate in VLBW infants when replacing the UVC with the PICC at 72 hours of age versus at seven days.

Materials and Methods: VLBW infants with UVC placed at admission and clinically stable for three days were randomly assigned to receive early replacement with PICC at 72 hours of age as the 72-hour group, or at seven days as the 7-day group. The primary outcome was the CLABSI rate. The secondary outcomes were the time from birth to CLABSI and any other complications.

Results: Fifty infants in the 72-hour group and 51 infants in the 7-day group were enrolled. The overall incidence of CLABSI was 10% in the 72-hour group and 27.4% in the 7-day group (RR 2.74, p=0.03). There were 4.6 CLABSIs per 1,000 catheter-days in the 72-hour group and 13.4 CLABSIs per 1,000 catheter-days in the 7-day group (p=0.02). The other complications and mortality rates were not significantly different.

Conclusion: The early removal of a UVC and replacement with a PICC by 72 hours of age significantly decreased the CLABSI rate compared to the routine replacement of the UVC at seven days of age.

Keywords: Very low birth weight; Umbilical venous catheters; Peripherally inserted central catheter; Central venous catheter; Central line-associated bloodstream infection

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Central venous catheters (CVCs), such as umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs), are frequently used in neonatal intensive care units (NICUs) to deliver fluids, medications, and parenteral nutrition to critically ill infants, especially very low birthweight (VLBW) and extremely low birth weight (ELBW) neonates. Central line-associated bloodstream infection (CLABSI), with a reported incidence ranging from 3% to 20%, is the most common serious adverse event[1-4], and it is associated with higher rates of poor neurodevelopmental outcomes and a higher risk of mortality[5,6]. In VLBW neonates, UVCs are usually inserted in the first day of life, and replacement intravenous access can be attained via PICCs if ongoing central access was required.

There is little evidence about the influence of the type of catheter used and the duration of the catheter on the CLABSI incidence. The U.S. Centers for Disease Control and Prevention (CDC), Hospital Infection Control Practices Advisory Committee currently recommends that UVCs should be removed as soon as possible when no longer needed but they can be left in place for up to 14 days if managed aseptically[1]. There is no current consensus in the literature regarding the CVC duration as a risk factor for CLABSI, and a threshold dwell time has not been established beyond which a UVC or PICC should be

Correspondence to:

Thanomsingh P.

Department of Pediatrics, Maharat Nakhon Ratchasima Hospital, Chang-Phueak Road, Mueang, Nakhon Ratchasima 30000, Thailand.

Phone: +66-81-7903405

Email: pthanomsingh@gmail.com

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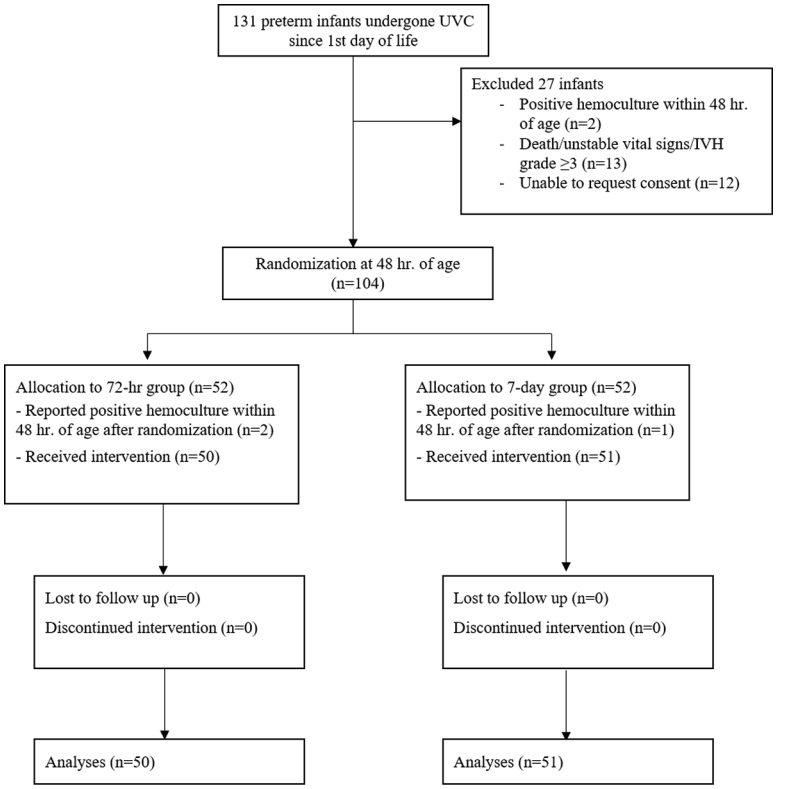

Figure 1. Flow diagram of the study.

routinely replaced. Furthermore, it is unclear whether early or late PICC insertion for UVC replacement has an impact on PICC CLABSI rates. Standard clinical practice in neonatal units is to remove or replace UVCs before 14 days, and often by seven days.

The aim of the present study was to compare the effectiveness of early replacement of UVCs with PICCs within 72 hours of age versus seven days in preventing CLABSI in VLBW preterm infants.

Materials and Methods

The present trial was conducted between April 2018 and May 2019 in a neonatal unit at Maharat Nakhon Ratchasima Hospital (MNRH), a tertiary neonatal center. The present study was approved by the MNRH Institutional Board Review (EC number 031/2018).

Studied infants were the premature infants who had a UVC placed on NICU admission that were clinically stable during three days of age and were planning to use CVCs for more than seven days. Infants with positive hemoculture within 72 hours of age, unstable vital signs requiring more than three inotropic drugs, up to grade III IVH, or had major congenital anomalies were excluded.

Study intervention and cointervention: After screening and enrollment with parental consent during the first three days after birth, premature infants with UVCs in place from the first day of age were randomized to replace with PICCs at three days of age for the 72-hour group or at seven days of age for the 7-day group (Figure 1). Randomization, with an allocation ratio of 1:1 and block sizes of 2, 4, or 6 were executed via a web-generated, block randomization sequence (www.sealedenvelope.com) and stratified according to birth weight at less than 1,000 g and 1,000 to 1,500 g. The randomization lists were stored in sealed, opaque envelopes at the neonatal unit. The subjects were allocated to a study group by the clinical team opening an opaque randomization envelope after obtaining informed consent. Infants in the 72-hour group had their UVCs replaced with PICCs at three days of age and for the 7-day group infants, the UVCs remained in place for up to seven days and were then replaced with PICCS if central line access was still required.

Placement of a UVC was attempted in infants of less than 1,500 g requiring a UVC on admission to the NICU. A single lumen catheter (3.5 F diameter, Vygon, Ecouen, France) was inserted under sterile

conditions by a Pediatrics Resident. All UVCs had continuous infusion of solutions in the main port. All catheter connections were checked hourly to guard against any disconnection. Both infusion and flush solutions contained heparin at 1.0 IU/mL for infants of 1,000 g or heavier and 0.5 IU/mL for infants lighter than 1,000 g or on total parenteral nutrition (TPN). Catheter placement was confirmed with chest and abdominal radiographs. Catheters were sutured in place into the umbilical cord, and tape was then used to secure the catheter to the infant's abdomen.

Placement of the PICC was performed under sterile conditions by neonatologists or pediatrics residents. A 20 cm catheter with a 24-gauge introducer needle (Vygon, Ecouen, France) was inserted in the infant's basilic, cephalic or axillary vein. PICC placement was confirmed radiographically to ensure that the final placement was within the central circulation, preferably at the right atrial/superior vena cava junction. The catheter and the proximal portion of the extension set were secured to the skin by using a sterile, transparent, and occlusive dressing. Solutions infused through the PICCs contained heparin, at the same concentration as for the UVC, and ran at a minimum rate of 1.0 mL/hour. PICCs were not used for rapid medication infusions, blood product administration, or blood drawing. The intravenous tubing was secured well to the skin, and the dressing integrity was assessed routinely and documented. The PICC site was checked, and its condition was documented hourly.

PICCs were discontinued when the infant had approached feeding of 100 to 120 mL/kg/day or the infants developed complications such as catheter occlusion, CLABSI, migration/dislodgment, phlebitis, mechanical damage to the catheter, pericardial effusion, pleural effusion, extravasation, or cardiac arrhythmia according to the physician's decision.

Umbilical artery catheters (UACs) were placed at the same time as the UVCs and used for blood gas or laboratory sample analysis and were removed as soon as possible if no indication for their use remained. All complications and the problems with each catheter were recorded until removal of the central catheter. The infants in both groups received oral fluconazole prophylaxis until the CVCs were removed. All decisions pertaining to the diagnosis and treatment and removal of the UAC and PICCs were at the discretion of the clinical team.

Outcomes

The primary outcome was the CLABSI defined as lab-confirmed blood stream infection with central line in place for at least two consecutive days and until the day after removal from the body. Lab-confirmed blood stream infection was the presence of bacteria or fungus in one or more blood cultures obtained from a symptomatic infant such as temperature instability, increased ventilator settings, increased apnea, bradycardia or desaturations, feeding intolerance, lethargy, or blood pressure instability. Infants who had a clinical picture consistent with sepsis and positive blood culture before 72 hours of age were diagnosed with early-onset sepsis (EOS) and were excluded from the present study.

All infants who had clinical signs consistent with sepsis underwent blood culture from peripheral vein. Whole blood of 0.5 to 1.0 mL was placed in sterile tubes and transported to the microbiology laboratory. The blood was streaked onto blood and chocolate agar plates and then incubated under aerobic conditions for five days. Organisms isolated by the culture systems were identified by using standard microbiologic techniques. The causative pathogen was the organism cultured during the first episode of CLABSI of any CVCs.

Secondary outcomes included the time to first CLABSI (from birth), necrotizing enterocolitis (NEC), days to full feeds, bronchopulmonary dysplasia (BPD), death, and complications of CVCs such as catheter obstruction, leaking, phlebitis, emboli, thrombosis, hemorrhage, arrhythmia, pericardial effusion, pleural effusion, and catheter rupture.

Statistical analysis

The primary outcome was CLABSI expressed as the number of episodes per 1,000 catheter-days. In defining the time to first CLABSI, an infant was considered to be at risk for CLABSI only while the catheter was in place. If the catheter was discontinued, the time to infection was censored at the time of discontinuation.

The authors estimated that a total enrollment of 104 infants was needed to detect a reduction in the incidence of infection from 58% to 30% based on the historical baseline medical records of the authors' institute, with 80% power and 5% significance.

All statistical analyses were performed by using Stata, version 14 (StataCorp LP, College Station, TX, USA). The data were analyzed by intention to treat. The incidence rate ratio (IRR) and Kaplan-Meier cumulative hazard functions were used where appropriate to compare the CLABSI

Table 1. Baseline characteristics of the infants

Characteristics	72-hour group (n=50)	7-day group (n=51)
Gestational age at birth (week); mean [SD]	28.7 [2.1]	28.4 [2.3]
Birth weight (g); mean [SD]	1,076.7 [225.0]	1,067.9 [236.6]
Male; n (%)	33 (66.0)	30 (58.8)
RDS; n (%)	50 (100)	51 (100)
Endotracheal intubation at birth; n (%)	38 (76.0)	37 (72.5)
Received surfactant therapy; n (%)	35 (70.0)	33 (64.7)
Total days of antibiotics in the first week (day); mean [SD]	6.6 [1.1]	6.9 [0.5]
Received Antibiotics in the first 7 days; n (%)	50 (100)	51 (100)
Ampicillin	50 (100)	51 (100)
Gentamicin	50 (100)	51 (100)
Cefotaxime	32 (64.0)	27 (52.9)
Amikacin	19 (38.0)	21 (41.2)
Meropenem	9 (18.0)	11 (21.6)
Vancomycin	7 (14.0)	8 (15.7)
Ampicillin/sulbactam	2 (4.0)	1 (2.0)
Colistin	3 (6.0)	6 (11.8)
Metronidazole	1 (2.0)	1 (2.0)

RDS=respiratory distress syndrome; SD=standard deviation

risks. Normally distributed continuous outcomes were analyzed by using the independent t-test. The Mann-Whitney rank-sum test was used to compare the groups with respect to nonnormally distributed or ordinal outcomes. Categorical data were analyzed by the exact probability test or Pearson chi-square, as appropriate. Two-tailed p-values of less than 0.05 were considered statistically significant for all analyses.

Results

One hundred thirty-one infants were assessed for eligibility between April 2018 and May 2019, among these 27 were ineligible as two infants had a positive hemoculture within 48 hours of age, 13 infants had unstable vital signs or had severe IVH of grade 3 or higher, and 12 infants could not get informed consent. Three infants were excluded after randomization because of positive hemoculture within the first 72 hours of age. The remaining 101 infants were enrolled and randomly assigned, with 50 infants allocated to the 72-hour PICC replacement group as the 72-hour group and 51 infants allocated to the 7-day PICC replacement group as the 7-day group.

Table 1 shows the demographic characteristics of the two groups. Similar numbers of infants in each group were male, RDS, required invasive ventilatory support, and received surfactant therapy. The mean birth weight and gestational age were similar in the two groups. They received similar treatment such as antibiotics and parenteral nutrition. All PICCS were inserted in upper extremities. UACs were inserted in 40 patients in 72-hour group and 43 patients in 7-day group for blood gas and laboratory samples analyses.

There were 21 positive hemocultures over the course of the present study that were associated with protocol-defined CLABSI in 19 infants (Table 2). The overall incidence of CLABSI was different between the groups at 10% in the 72-hour group and 27.4% in the 7-day group (p=0.03). Infants in the 72-hour group had 4.6 CLABSIs per 1,000 catheter-days, whereas those in the 7-day group had 13.4 CLABSIs per 1,000 catheter-days (IRR 2.9, 95% CI 1.1 to 9.1, p=0.02). Total CVC dwell time was not different between the two groups. In the 72-hour group, the infants had a longer duration of PICCs in place for a median of 18 days (IQR 13 to 27), but it was not significantly different (p=0.06). Time to first CLABSI was significantly different between the two groups (p=0.02). A Kaplan-Meier plot for the first CLABSI demonstrated that the 7-day group had a higher rate of CLABSIs and an earlier rise than the 72-hour group (Figure 2). The longest duration of CVCs was 79 days in the 72-hour group. Almost all of CLABSIs in 72-hour group developed in the first nine day and there was only one CLABSIs that developed on the twenty-second day. The most common isolated pathogens of first CLABSIs were gram-negative organisms such as Acinetobactor baumanii and Klebseilla pnuemoniae. Two patients had second CLABSIs and the isolated

Table 2. Primary outcome and the outcomes of central catheters

Clinical characteristics	72-hour group (n=50)	7-day group (n=51)	p-value
Duration of UVC (day); median (IQR)	3 (3, 3)	7 (6, 7)	<0.001
Duration of UAC (day); median (IQR)	5 (4, 6)	7 (5, 7)	0.0003
Duration of umbilical catheters (day); median (IQR)	4.5 (3, 6)	7 (7,7)	<0.001
Duration of PICC (day); median (IQR)	18 (13, 27)	13 (9, 22.5)	0.06
Total duration of central line (day); median (IQR)	19.5 (14, 29)	19 (14, 27)	0.57
Number of patients with positive hemoculture	5	14	0.04
Episode of CLABSI	6	15	
Total catheter-days	1,297	1,119	
CLABSI rate per 1,000 catheters-days	4.6	13.4	0.02
Isolated pathogens from 1st CLABSI			
Acinetobacter baumanii	1	5	
Klebsiella pneumoniae	1	5	
Coagulase-negative staphylococcus	2	3	
Candida spp.	1	1	
Isolated pathogens from 2nd CLABSI			
Coagulase-negative staphylococcus	1	1	
Complications of central line	7	4	0.53
Obstruction	4	2	
Leakage	3	2	

UVC=umbilical venous catheter; UAC=umbilical artery catheter; PICC=peripherally inserted central catheter; CLABSI=central line-associated bloodstream infection; IQR=interquartile range

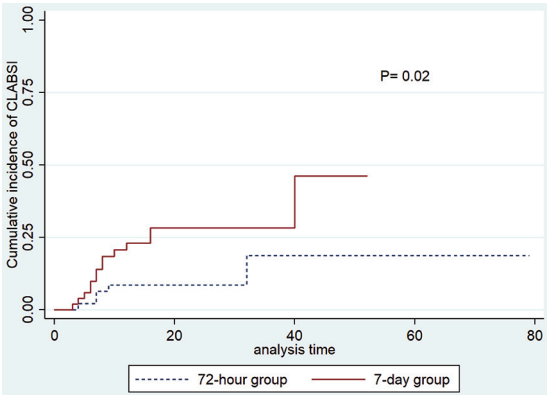

Figure 2. Kaplan-Meier estimates of hazard function for the first CLABSI between replacement of the UVC with a PICC at 72 hours of age and at 7 days of age.

pathogen was coagulase-negative staphylococcus. There were no differences between the groups in the number of days to achieve full feedings, total duration of TPN, rate of NEC, length of stay, BPD, or death. Other complication of PICCs were catheter obstruction and leaking. There was no difference between the two groups (Table 3).

Discussion

CLABSI is the most prevalent and important problem of premature infants who have CVCs in place. The strategy to decrease this complication is to remove CVCs as soon as possible.

In the present study, early replacement of UVCs with PICCs at 72 hours of age decreased CLABSI rates significantly compared to replacement at 7 days at 4.6 versus 13.4 per 1,000 catheter-days. This was different from the previous WHO recommendations for using UVCs until 7 to 14 days of age[1]. The CLABSI rate in the 7-day group increased by Day 4, doubled by Day 6 and trended to increase until 20 days of age, but in the 72-hour group, the CLABSI rate was lower and after the ninth day of age, there was only one case with CLABSIs.

From a previous study, one of the risk factors for developing CLABSI was the indwelling time of CVCs[7-11]. In the present study, the total CVC duration, including the duration of the UVC and PICC, was not different between the two groups but the incidences of CLABSI were different. In the 72-hour group, having replacement of the UVC with a PICC at Day 3 of age, they had longer duration of PICCs but their incidences of CLABSI were significantly lower. These findings support the benefit of early elective replacement of UVC with PICCs within 72 hours of life.

The type of CVCs and the duration of UVCs

Table 3. Clinical outcomes and mortality

Outcomes	72-hour group (n=50)	7-day group (n=51)	p-value
Duration of invasive respiratory support (day); median (IQR)	4.5 (2, 10)	7.5 (4, 20)	0.13
Duration of oxygen supplementation (day); median (IQR)	20.5 (4, 36)	24 (8, 56)	0.06
Days to full feeding (day); median (IQR)	21 (17, 29)	26 (17, 34)	0.34
Total TPN days (day); median (IQR)	18 (13, 24)	17 (12, 29)	0.95
BPD; n (%)	20 (40.0)	22 (43.1)	0.84
PDA; n (%)	33 (66.0)	28 (54.9)	0.31
Surgical PDA; n (%)	5 (10.0)	6 (11.8)	1.00
NEC ≥2; n (%)	6 (12.0)	8 (15.7)	0.77
Death; n (%)	9 (18.0)	12 (23.6)	0.63
BPD or death; n (%)	27 (56.0)	31 (60.8)	0.55
Length of stay (day); median (IQR)	50 (29, 77)	49.5 (33, 79)	0.82

TPN=total parenteral nutrition; BPD=bronchopulmonary dysplasia; PDA=patent ductus arteriosus; NEC=necrotizing enterocolitis; IQR=interquartile range

have been studied as risk factors for CLABSI. Many previous studies concluded that different types of CVCs did not affect the incidence of CLABSI[3,10,12-15], Shalibi et al. demonstrated that the use of UVCs only from Day 1 or PICCs only from Day 1 or those who received a UVC and were then changed for a PICC did not have different rates of CLABSI[13]. There is only one RCT study comparing the rate of CLABSI between short-term UVC for UVCs seven to ten days followed by PICCs, and long-term UVC use, for up to 28 days, revealed no difference in CLABSI rates[12]. There are other studies comparing the rates of CLABSI between UVCs and PICCs only from Day 1. They did not show any differences in CLABSI[10,13-15]. However, almost all of these studies were observational studies, and the indication for CVCs and the condition of patients needing CVCs might be different, leading to uncertain conclusions. One retrospective analysis from Australian NICU data showed an increased risk of CLABSI from Day 4 of UVCs, and the subgroup analysis showed early UVC removal and PICC replacement before four days was associated with a trend of lower CLABSI rate in the first PICC[14]. These findings support the benefit of their current practice of the early removal of UVCs, consistent with the outcomes of the present study.

The reason for decreasing CLABSI rates after the early replacement of UVCs might be the lower rate of bacterial colonization of PICCs than UVCs. Sobczak et al. demonstrated 100% bacterial colonization in umbilical catheters of preterm infants regardless of antibiotic use or dwell time of catheterization and concluded that umbilical catheters are vectors for skin microflora transmission to the bloodstream via biofilm formation[16]. From the study of Konstatini et al., the rate of CLABSIs in VLBW infants who had UVCs or PICCs only was not different, but the rate of positive cultures from tip colonization of UVCs was significantly higher than that from PICCs[15]. Arnts et al. also demonstrated microorganism colonization in the umbilical stump from the first day of life[3]. The early removal of UVCs and replacement with PICCs in patients who need CVCs may allow the patients to benefit from lower bacterial colonization.

UAC was also considered as one of the central lines. In the present study, 40 patients in 72-hour group and 43 patients in 7-day group had UACs since birth for blood gas and laboratory sample analyses and were removed if no indication for their use remained according to clinical team decision. The median duration of UACs in the 72-hour group was significantly shorter than in the 7-day group and the median duration of invasive respiratory support of 4.5 days (IQR 2, 10) in the 72-hour group was insignificantly shorter than 7.5 days (IQR 4, 20) in the 7-day group (p=0.13). The total duration of umbilical catheters in the 72-group was also significantly shorter than in the 7-day group with a median duration of 4.5 days (IQR 3, 6) in the 72-hour group and seven days (IQR 7, 7) in the 7-day group (p<0.001). These may be the benefit of early removal of UVC to improve clinical condition and not requiring longer use of UAC or may be the confounding factor of earlier removal of UAC leading to decreasing CLABSIs in the 72-hour group. To clarify the effect of UAC dwell time for reducing CLABSI rate, additional well-designed randomized clinical trial will be needed.

The present study has limitations. This was a single-center study. The present study center has

crowded patients, less antenatal corticosteroid administration, and a high rate of endotracheal intubation at birth, leading to a higher rate of LOS than other units. However, based on the study, the CLABSI rate can be decreased by early replacement of UVCs with PICCs and removal of UACs as soon as possible. Routine removal of umbilical catheter at seven to 14 days may increase risk of CLABSI.

The authors performed echocardiography only in patients with indications and did not perform routine echocardiography to detect catheter complications in every patient.

Conclusion

The present study confirms the benefit of early replacement of UVCs with PICCs in the first three days after delivery and remove UACs as soon as possible to decrease the CLABSI risk, and this strategy may decrease other long-term complications, such as BPD or death.

What is already known on this topic?

The CVCs dwell time is a major risk factor for CLABSI. Standard clinical practice in neonatal units is to remove or replace UVCs before 14 days, and often by seven days.

What this study adds?

The present study confirms the benefit of early replacement of UVCs with PICCs in the first three days after delivery and remove UACs as soon as possible to decrease the CLABSI risk. Routine removal of umbilical catheter at seven to 14 days may increase risk of CLABSI.

Conflicts of interest

The authors declare no conflict of interest.

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