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Pediatrics 2006;118:e25-e35; originally published online Jun 19, 2006;
DOI: 10.1542/peds.2005-1880

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<http://www.pediatrics.org/cgi/content/full/118/1/e25>

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American Academy of Pediatrics

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A Randomized Trial Comparing Long-term and Short-term Use of Umbilical Venous Catheters in Premature Infants With Birth Weights of Less Than 1251 Grams

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

BACKGROUND. Umbilical vein and percutaneous central venous catheters are often used in preterm infants, but they can lead to complications, including infection.

OBJECTIVE. We hypothesized that long-term umbilical vein catheter use would result in fewer infections than short-term umbilical vein catheter use followed by percutaneous central venous catheter placement.

DESIGN/METHODS. Infants ≤ 1250 g with umbilical vein catheters placed at admission were randomly assigned to a long-term (umbilical vein catheter up to 28 days) or short-term (umbilical vein catheter for 7–10 days followed by percutaneous central venous catheter) group. Catheter infection was defined as symptoms and ≥ 1 positive blood culture for definite pathogens or >1 positive culture for other organisms, with a catheter in place. Clinically significant echocardiogram findings were defined as thrombi threatening vascular occlusion, crossing/blocking heart valves, or otherwise felt to be significant by the cardiologist. The primary outcome was time from birth to catheter infection, analyzed by the log-rank test.

RESULTS. There were 106 subjects in the short-term group and 104 in the long-term group with birth weights of 915 ± 198 and 931 ± 193 g and gestational ages of 27.8 ± 2.0 and 27.7 ± 2.2 weeks, respectively. The distribution of time to catheter infection did not differ between the groups. The overall incidence of catheter infection was 13% in the short-term group and 20% in the long-term group. Median age at catheter infection was 11.5 days in the short-term group and 14 days in the long-term group. There were 7.4 infections per 1000 catheter-days in the short-term group and 11.5 per 1000 in the long-term group. Seven infections in the short-term group were in umbilical vein catheters, and 18 infections in the long-term group were in umbilical vein catheter. Echocardiograms detected 4

www.pediatrics.org/cgi/doi/10.1542/peds.2005-1880

doi:10.1542/peds.2005-1880

Key Words

bacteremia, septicemia, thrombosis, central venous catheterization, very low birth weight infant

Abbreviations

UVC—umbilical venous catheter
 PCVC—percutaneous central venous catheter
 NEC—necrotizing enterocolitis
 EKG—electrocardiogram
 SGA—small for gestational age

Accepted for publication Jan 13, 2006

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

infants in the short-term group and 7 infants in the long-term group with significant thrombosis. All significant thrombi were at the site of the umbilical vein catheter tip. No thrombus caused hemodynamic compromise, no child had clinical symptoms of thrombosis, and none required therapy. Of the 45 small-for-gestational-age infants in the study, 9 developed thrombi (short-term group, 4; long-term group, 5). The incidence of thrombi was higher in the small-for-gestational-age group (20%) versus other study subjects (9%). There were no differences in time to full feedings or to regain birth weight or in the incidence of necrotizing enterocolitis or death.

CONCLUSIONS. Infection and complication rates were similar between infants managed with an umbilical vein catheter in place for up to 28 days compared with infants managed with an umbilical vein catheter replaced by a percutaneous central venous catheter after 7 to 10 days. Umbilical vein catheter durations beyond the current Centers for Disease Control and Prevention–recommended limit of 14 days may be reasonable.

UMBILICAL VENOUS CATHETERIZATION is a common procedure in the management of sick neonates. These catheters are most commonly used for the administration of fluids, nutrition and medications, blood gas monitoring, central venous pressure monitoring, and exchange transfusions. However, use of an umbilical venous catheter (UVC) can lead to serious complications including thrombosis, embolization, hemorrhage, arrhythmias, effusions, portal hypertension, and sepsis.¹⁻⁷

Because the risk of complications may increase with duration of use,⁴ UVCs are often removed after relatively short periods and replaced with percutaneous central venous catheters (PCVCs) for maintenance of long-term fluid and nutritional status. PCVCs also have associated risks and complications including dislodgment, obstruction, infiltration, broken or leaking lines, thrombus, effusions, and sepsis.⁸⁻¹² Infection of these catheters has become a major concern in neonates.⁸⁻¹³

The risk profiles of a long-term UVC to a long-term PCVC have seldom been compared.^{4,14-16} On the basis of these limited data, the Centers for Disease Control and Prevention currently recommend use of UVCs be limited to 14 days.¹⁷ However, a survey of nursery directors revealed that some NICUs leave UVCs in place for a longer period of time.¹⁸ In a retrospective review of 230 infants with birth weights <1251 g who were admitted to our NICU and required a UVC and/or PCVC, the apparent proportion of catheters remaining infection-free at 20 days (the time at which the last UVC was removed) was 89% for UVCs and 73% for PCVCs. In this study, we prospectively examined catheter-related bacteremia and associated complications in long-term use of

UVCs compared with short-term use of UVCs followed by replacement of these catheters with PCVCs. We hypothesized that long-term use of UVCs would present fewer infections and other risks than short-term use of these catheters followed by long-term use of PCVCs.

METHODS

Subjects

The trial was conducted between July 1998 and February 2004 in a single 52-bed tertiary referral NICU. The University of Rochester Institutional Review Board approved the study. Infants with birth weights ≤ 1250 g who had a UVC placed on NICU admission were eligible for the study. Infants who required a UVC for exchange transfusion, infants with gastrointestinal abnormalities including gastroschisis and omphalocele, or infants with congenital heart disease with intracardiac shunting were excluded. Infants born at <24 weeks' gestation or <500 g at birth were eligible, but for these infants the attending neonatologist was first consulted and had to provide approval. The parents or legal guardians of the patients gave informed consent before enrollment.

Umbilical Catheterization

Placement of a UVC was attempted in infants ≤ 1250 g on admission to the NICU. Either a single- or double-lumen catheter (3.5F or 5.0F diameter, Argyle Catheter; Tyco Healthcare, Mansfield, MA) was inserted under sterile conditions. A double-lumen UVC was used if it was technically possible to place one. Care of the catheters was standardized. Catheters were attached to transducers, which were calibrated every 8 hours. The entire system, including the transducer, was changed every 24 hours if the infused concentration of dextrose was >12.5 g/L and every 72 hours for concentrations of dextrose ≤ 12.5 g/L. All UVCs had continuous infusion of solutions in the main port, with flushes every 4 hours in the secondary port if one was present. Both infusion and flush solutions contained heparin (1.0 IU/mL for infants >1000 g and 0.5 IU/mL for infants ≤ 1000 g or on total parenteral nutrition). All catheter connections were checked hourly to guard against any disconnection. Catheter placement was confirmed with a chest and abdominal radiograph. The catheter placement was adjusted to place the catheter tip at the inferior vena cava/right atrial junction. Catheters were sutured in place into the umbilical cord, and tape was then used to secure the catheter to the infant's abdomen. If a UVC needed to be replaced (because it fell out, slipped into improper position, or stopped working) and it was ≤ 7 days old, the catheter could be replaced at the discretion of the clinical team.

Percutaneous Central Venous Catheterization

Placement of the PCVC was performed under sterile conditions, and care of the catheters was standardized.

Either an 8- or 20-cm catheter with a 24-gauge introducer needle (L-Cath; Becton Dickinson Infusion Systems Inc, Sandy, UT) was inserted in the infant's brachial, axillary, saphenous, or external jugular vein. PCVC placement was confirmed radiographically to ensure that final placement was within the central circulation, preferably at the right atrial/superior vena cava junction for brachial, axillary, and external jugular catheters and in the inferior vena cava for catheters placed in the saphenous vein. A small-bore extension set was then connected to the PCVC in a sterile manner. These sets remained on the lines indefinitely. The catheter and the proximal portion of the extension set were secured to the skin by using a sterile, transparent, occlusive dressing. Solution infusing through the PCVC contained heparin (at the same concentrations as for UVC) and ran at a minimum rate of 1.0 mL/hour. PCVCs were not used for rapid medication infusions or blood product administration. Blood was not drawn from the PCVC unless sepsis was suspected and PCVC cultures were necessary. Sterile gloves were worn during all solution changes. Intravenous tubing was secured well to the skin but did not occlude any part of the catheter dressing. Dressing integrity was assessed routinely and documented. Dressings were changed when there was loss of adhesiveness or drainage at the site or when they became too restrictive. The PCVC site was checked and its condition documented hourly. A dedicated team of neonatal fellows, nurse practitioners, and physician assistants performed all dressing changes and catheter manipulations.

Study Intervention

Parents were approached for study consent during the first 7 to 10 days after the infant's birth. Although there was no minimum time that a UVC could remain in place, parents were only approached if it was anticipated that a central catheter would be required beyond 7 days. If parents gave permission, infants were randomly assigned to the long-term (long-term UVC) or short-term (short-term UVC followed by PCVC) group. Subjects were block-randomized in groups of 10 in 2 strata (≤ 1000 and > 1000 g birth weight). The randomization scheme and envelopes were prepared by one of the investigators (M.B.-O.) using a random-number table. Block size was not revealed to the clinical team. Subjects were allocated to a study group by the clinical team opening an opaque randomization envelope after obtaining informed consent. Study-group assignments were not masked. Only the type of access was dictated by the study protocol. The clinical team made decisions about overall duration of central access. Central catheters were discontinued when the infant no longer required total parenteral nutrition, had approached full feeding, and/or had alternate peripheral intravenous access.

In the short-term group, the UVC remained in place

up to 7 to 10 days of age. If central access was necessary beyond day 10, PCVC placement was attempted beginning at day 7 to assure successful placement by day 10. The decision regarding the necessity of the PCVC was left to the infant's team of care providers. The UVC remained in place until the PCVC was established. The PCVC remained in place until removal at the discretion of the clinical team. If a PCVC was removed for any reason and further central access was required, another PCVC was placed. All complications and problems of each catheter were recorded until removal of the final central catheter.

In the long-term group, the UVC was placed on admission as described. When the catheter was no longer needed or by 28 days at the latest, the catheter was removed. At that time, if the infant was not close to full feedings and required central access, a PCVC was placed at the discretion of the team. If a PCVC was removed for any reason and further central access was required, another PCVC was placed. All complications and problems of each catheter were recorded until removal of the final central catheter.

Monitoring/Data

In addition to the primary outcome, catheter-related infection, all infants were monitored for a number of secondary outcomes including both catheter-related risks and potential benefits. These outcomes included emboli, thrombosis, hemorrhage, arrhythmia, pericardial effusion, pleural effusion, necrotizing enterocolitis (NEC), catheter rupture, mechanical catheter stability, catheter longevity, days to full feeds, episodes of feeding intolerance, and days to regain birth weight. Feeding intolerance was defined as gastrointestinal symptoms (gastric residuals, increased abdominal girth, emesis, abnormal radiograph, or heme-positive stools) that caused at least 2 consecutive feedings to be held.

All infants had a baseline electrocardiogram (EKG) performed at study entry. Repeat EKGs were performed if an arrhythmia was detected at any time during the study. EKGs were performed before and after discontinuing or manipulating any central catheter that was believed to be causing an arrhythmia.

Echocardiography

Echocardiograms of all infants with UVCs and PCVCs were performed to monitor for thrombi. The echocardiogram was also used to help determine, when possible, position of the catheter, presence of pericardial effusions, and any changes in right heart function. In addition, the initial echocardiogram included a full clinical evaluation of the heart to rule out structural heart disease.

Echocardiograms in the short-term group were performed at study entry, before removal of the UVC at 7 to 10 days of age, on placement of the PCVC, at 7 and 21 days after PCVC placement (± 1 day), and 1 to 2 weeks

after the PCVC was discontinued. In the long-term group, echocardiograms of the UVC were performed at study entry, 7, 14, and 28 days of age (± 1 day), before removal of the UVC, and 1 to 2 weeks after the catheter was removed; for those requiring a PCVC, echocardiograms of the PCVC were performed at catheter placement, 7 and 21 days (± 1 day), and 1 to 2 weeks after the catheter was discontinued. If a catheter was removed after 14 but before 28 days of age, an echocardiogram was performed before catheter removal. Study echocardiograms due within 4 days of a previous echocardiogram (either study or clinically indicated) were deferred.

Given that portal vein thrombosis with subsequent portal hypertension has been reported as presenting months to years after UVC placement⁴ and because late vascular occlusion has also been reported with other central venous catheters,⁷ 5 years of follow-up were planned to determine any long-term complications. This was conducted through a contact with the child's pediatrician (yearly for 5 years) to assess any potential signs of portal hypertension, liver disease, abnormal bleeding, esophageal varices, or ascites. An echocardiogram was also planned at age 4 to 5 years in all subjects to assess the major thoracic and hepatic vessels. These evaluations are ongoing, and results beyond 1 year will not be reported here.

Evaluation for Infection

All infants who had a sepsis workup performed during the study period (until 28 days or until catheter removal, whichever came first) had simultaneous quantitative peripheral and catheter blood cultures performed. Whole blood (0.3–1.0 mL) was placed in sterile Isolator (Wampole, Cranberry, NJ) tubes and transported to the microbiology laboratory. Blood was streaked onto blood and chocolate agar plates and then incubated for 5 days under aerobic conditions. In instances in which simultaneous quantitative cultures could not be drawn (eg, no blood return from the catheter), whole blood (0.3–1.0 mL) was collected in aerobic blood-culture bottles (Biomerieux, Durham, NC), which contain carbon dioxide-sensitive indicators. Culture bottles were placed in an automated reader (Bact-alert; Biomerieux) that read carbon dioxide levels every 10 minutes. Any positive or potentially positive cultures were Gram-stained, streaked onto blood and/or chocolate agar plates (depending on the likely pathogen), and incubated under aerobic conditions. Organisms isolated by using either culture system were identified by using standard microbiologic techniques.

Definitions

Infection

The definition of infection included symptomatology (eg, temperature instability, increased ventilator set-

tings, increased apnea, bradycardia or desaturations, feeding intolerance, lethargy, or blood pressure instability) and either a single positive blood culture for prospectively defined definite pathogens or multiple positive cultures (≥ 2 within 48 hours) for other organisms from usually sterile site(s) (blood, catheter tip, urine, or cerebrospinal fluid, with at least 1 positive culture from the blood). Organism classification is listed in Table 1. Catheter-related infection was defined as infection while a catheter (UVC or PCVC) was in place. Each infant was counted only once as having catheter infection during the study regardless of future blood-culture results.

Clinically Significant Thrombi

A study cardiologist reviewed all echocardiograms. All findings were recorded, but during the course of the study the cardiologist reported only clinically significant findings to the clinical team. Clinically significant findings on echocardiogram were defined as any hemodynamically significant thrombi (threatened occlusion of major vessel, crossing or blocking heart valve) or any other finding felt by the reading cardiologist to pose a potential threat to the subject. Small thrombi on or adjacent to catheter tips not associated with arrhythmias or hemodynamic compromise were generally not reported. Thrombi were grouped by size as small (longest linear dimension: ≤ 5 mm), moderate (5.1–10 mm), or large (> 10 mm).

In the event of a clinically significant echocardiographic finding, the study cardiologist reported the finding to the investigator and the clinical team. The cardiologist also recommended a plan for further evaluation or follow-up of the abnormal finding. The clinical team made the final decision about the nature and extent of evaluation and follow-up. The study nurse, in consultation with the clinical team, tracked and/or arranged follow-up evaluations, including all outpatient visits necessary for evaluation of the abnormal findings. Reports of all follow-up evaluations were provided to the study nurse.

TABLE 1 Classification of Organisms Isolated From Blood Cultures

Pathogens ^a	Potential Pathogens ^b
<i>Candida albicans</i>	<i>Bacillus</i> species
<i>Escherichia coli</i>	<i>C glabrata</i>
Group B <i>Streptococcus</i>	<i>C parapsilosis</i>
<i>Klebsiella oxytoca</i>	Coagulase-negative <i>Staphylococcus</i>
<i>Pseudomonas aeruginosa</i>	<i>Corynebacterium</i>
<i>Staphylococcus aureus</i>	<i>Enterococcus</i>
<i>Stenotrophomonas maltophilia</i>	<i>Hafnia alvei</i>
	<i>M furfur</i>
	<i>Micrococcus</i>

^a Organisms for which a single positive blood culture was considered evidence of infection.

^b Organisms for which multiple positive cultures (≥ 2 within 48 hours) from usually sterile site(s) (blood, catheter tip, urine, or cerebrospinal fluid, with at least 1 positive culture from the blood) was considered evidence of infection.

Mechanical Complications

Additional severe mechanical complications were prospectively defined as embolus, hemorrhage, arrhythmia, pleural effusion, or broken catheter.

Statistical Analysis

The primary outcome variable was the time (from birth) until catheter-related infection. In defining this outcome, an infant was considered to be at risk for a catheter-related infection only while the catheter was in place. If the catheter was discontinued, the time to infection was censored at the time of discontinuation. If a catheter ceased functioning at any time before 28 days and was replaced, the infant was considered at risk for a catheter-related infection through 28 days as long as a catheter remained in place. Time to infection was censored at 28 days if the catheter remained in place after 28 days.

Before beginning the study, we estimated the number of subjects that would be required for an adequate examination of the hypothesis that long-term use of a UVC would present fewer infection risks than short-term use of a UVC followed by use of a PCVC. On the basis of the results of our retrospective review in infants <1251 g, the apparent proportion of catheters remaining infection-free at 20 days (the time at which the last UVC was removed) was 89% for UVCs and 73% for PCVCs. To detect a similar difference in a prospective study, with a 2-sided $\alpha = .05$ and a power of 80%, 105 subjects were needed per group.

Data were entered into an Access 2000 (Microsoft, Redmond, WA) database. Statistical analysis was performed by using Stata 6.0 (Stata Corp, College Station, TX) and SAS (SAS Institute, Cary, NC). The data were analyzed by intention to treat. The 2 treatment groups were compared with regard to the primary outcome variable by using the log-rank test. The distribution of time to infection was described by using Kaplan-Meier curves. Normally distributed continuous outcomes were analyzed by using the Student's *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 Fisher's exact test or Pearson χ^2 , as appropriate. Two-tailed *P* values of <.05 were considered statistically significant for all analyses.

RESULTS

Demographics

There were 537 infants assessed for eligibility, of whom 104 were ineligible, 150 had parents refuse to participate in the study, and 73 were excluded for other reasons (Fig 1). The remaining 210 infants were enrolled and randomly assigned, with 106 infants allocated to the short-term group and 104 infants allocated to the long-term group. Table 2 contains the demographic characteristics

of the 2 groups. Similar numbers of infants in each group were male, and racial origins were similar between groups. The mean birth weight and gestational age were similar in the 2 groups.

Primary Outcome

There were 155 positive blood cultures over the course of the study that were associated with protocol-defined catheter infections in 35 infants (Table 3). The primary outcome, the time to catheter-related infection, did not differ significantly between the long-term and short-term groups (Fig 2). The overall incidence of catheter sepsis (13% in the short-term group and 20% in the long-term group; *P* = .17) and the duration of catheter use before infection did not differ between groups (Table 4). Infants in the short-term group had 7.4 catheter-related infections per 1000 catheter-days, whereas those in the long-term group had 11.5 catheter-related infections per 1000 catheter-days. Seven infections in the short-term group were in UVCs, and 18 infections in the long-term group were in UVCs. The remainder of infections in each group were in PCVCs.

Number of Catheters Placed

In the short-term group, there were 113 UVCs placed by 28 days of age, with 99 infants having 1 UVC placed and 7 infants having 2 separate UVC placements. All but 1 short-term group subject had double-lumen UVCs placed. There were a total of 97 PCVCs placed by 28 days in the short-term group, with 69 infants having 1 catheter placed, 14 infants having 2 PCVCs placed, and 23 infants in whom a PCVC was not placed. In the long-term group, there were 147 UVCs placed by 28 days, with 69 infants having 1 UVC placed, 27 infants having 2 separate UVC placements, and 8 infants having a total of 3 separate catheter placements. All but 2 long-term group subjects had double-lumen UVCs placed. A total of 34 PCVCs were placed by 28 days in the long-term group, with 32 infants having 1 catheter placed, 1 infant having 2 PCVCs placed, and 71 infants in whom a PCVC was not placed. Overall, the total number of catheters placed in the short-term group exceeded the number placed in the long-term group (Table 4).

Complications

Thromboses

There were 24 infants with catheter-related thrombus detected on echocardiogram, 11 of whom had thrombi judged to be clinically significant on the basis of the cardiologist's evaluation (Table 4). None were obstructive or crossed heart valves. Six thrombi were moderate in size (5.1–10 mm), 5 of which were felt to be clinically significant, whereas 18 were small. There were no differences between groups in the number of thrombi or clinically significant thrombi (Table 4). No child had

FIGURE 1

Flow of participants through the trial. Of 104 potential subjects not meeting inclusion criteria, 99 had no UVC placed and 5 were ineligible for other reasons. Of 73 subjects not enrolled for other reasons, 25 had the UVC removed before approach for consent, 24 were not allowed to participate by the attending neonatologist, 6 had no parent available for consent, 2 had parents with a language barrier, and 16 parents were missed.

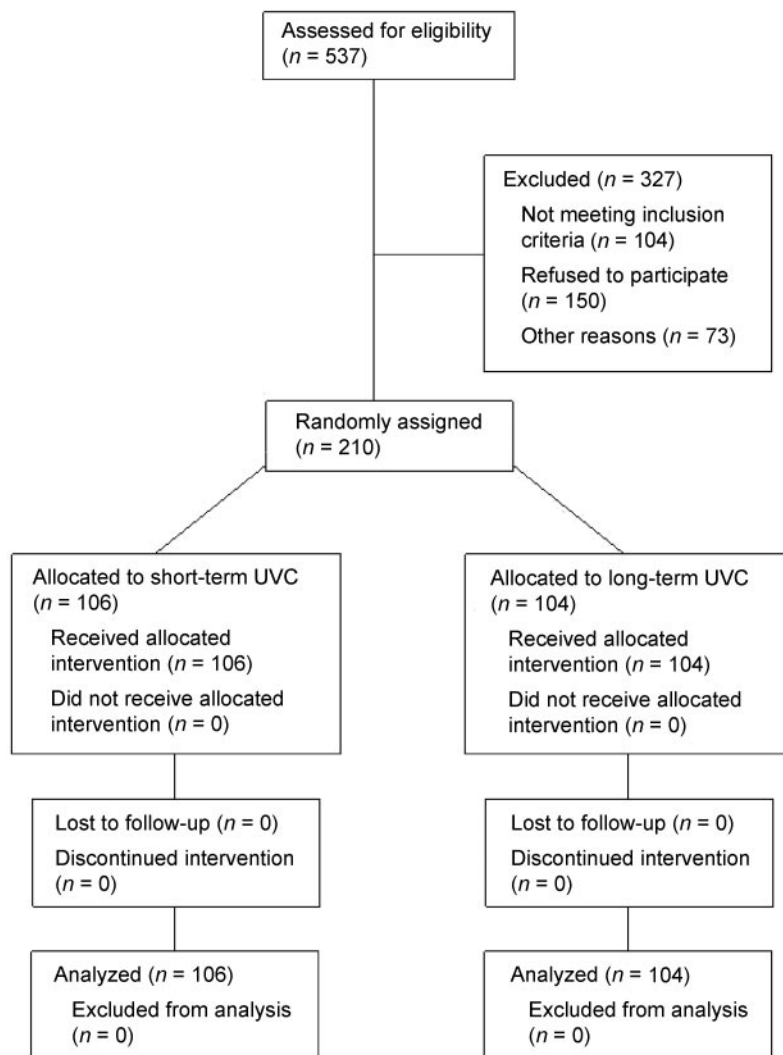


TABLE 2 Demographic Characteristics

	Short-term Group	Long-term Group
N	106	104
Male gender	54 (51)	58 (56)
Race		
White	67 (63)	59 (57)
Black	32 (30)	37 (36)
Other	7 (7)	8 (8)
Birth weight, g	915 ± 198	931 ± 193
Gestational age at birth, wk	27.8 ± 2.0	27.7 ± 2.2

Data presented as n (%) or mean ± SD.

clinical symptoms of thrombosis. One child in the long-term group had a catheter removed because of a moderate-sized thrombus present at the UVC tip. Echocardiographic evidence of thrombus persisted for a median of 16.5 days (range: 5–279 days). Eleven subjects had continued evidence of thrombus at the final recorded echocardiogram performed at 13 to 279 days (median: 28 days) after the initial positive study. Thirteen subjects

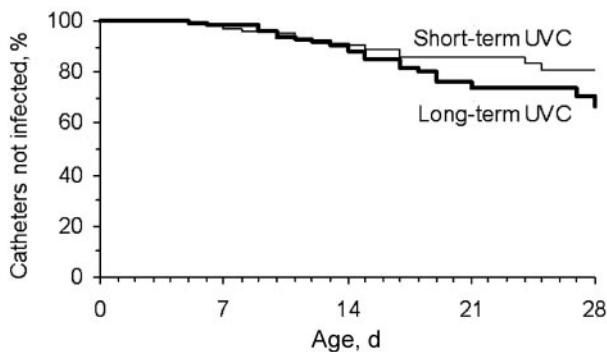
had echocardiographic confirmation of thrombus resolution on repeat echocardiograms performed from 9 days to 5 years (median: 49 days) after the initial positive study. All thrombi resolved without thrombolytic therapy.

Two small, nonsignificant thrombi (1 in the short-term group and 1 in the long-term group) were seen at the site of the PCVC tip in the superior vena cava. All other thrombi were at the site of the UVC tip. All UVC-tip thrombi were sessile or “sheath-like.” Eight UVC-related thrombi were in the right atrium, whereas the remainder were in the inferior vena cava. The 2 PCVC-tip thrombi were detected while the PCVC was in place (at 12 and 13 days after PCVC placement). UVC-tip thrombi were detected in 3 subjects while the catheter was in place (at 6, 11, and 23 days of age), whereas in 19 subjects thrombi were recognized at the catheter-tip site only at follow-up echocardiogram 1 to 2 weeks after UVC removal. For UVC-tip thrombi, the onset of the thrombus was defined either as the first time the throm-

TABLE 3 Number of Catheters and Pathogens

	Short-term Group	Long-term Group
Total No. of catheters		
UVC		
1	99	69
2	7	27
3	0	8
PCVC		
0	23	71
1	69	32
2	14	1
Pathogens in catheter-related infections		
<i>Calbicans</i>	2	0
<i>C parapsilosis</i>	0	1
Coagulase-negative <i>Staphylococcus</i>	8 ^a	12
<i>Enterococcus</i>	0	2
<i>E coli</i>	1	2
Group B <i>Streptococcus</i>	0	1
<i>K oxytoca</i>	1	0
<i>P aeruginosa</i>	1 ^a	1
<i>S aureus</i>	1	2
<i>S maltophilia</i>	1	0

^a One subject in the short-term group simultaneously met the definitions for *P aeruginosa* and coagulase-negative *Staphylococcus* catheter infections.



No. at risk					
Short-term	106	103	67	42	23
Long-term	104	101	67	37	19

FIGURE 2

Time to catheter infection. Data are presented as a Kaplan-Meier plot, with catheters remaining at 28 days censored at that time. Numbers of catheters remaining at each week are listed below the graph. The distribution of time to catheter infection did not differ between groups ($P = .19$).

bus was seen on echocardiogram or the date that the catheter was removed, whichever was earlier. UVC-tip thrombi occurred with a range of onset of 5 to 30 days of age and a median onset of 11 days.

Of the 210 infants enrolled, 45 were small for gestational age (SGA), defined as weight less than the 10th percentile.¹⁹ Of these 45 infants, 9 developed thrombi (4 in the short-term group, 5 in the long-term group). Five of these thrombi were defined as significant (3 in the short-term group, 2 in the long-term group). The incidence of thrombi was higher in the SGA group than in other study subjects (9 of 45 [20%] vs 15 of 165 [9%];

relative risk: 2.20; 95% confidence limits: 1.03, 4.69; $P = .04$).

Pericardial Effusions

Twenty-one infants developed a pericardial effusion (Table 3). There was no difference in the incidence of effusions between groups. All effusions were ≤ 1 to 2 mm in depth, and none resulted in hemodynamic compromise. Twelve of the effusions were seen while a catheter was in place: 9 with a UVC (3 in the short-term group, 6 in the long-term group) and 3 with a PCVC (3 in the short-term group). All effusions were considered to be incidental findings, and only one, detected on an echocardiogram during which no catheter was in place, was reported by the cardiologist to the clinical team.

Mechanical Complications

Only 1 subject suffered a severe mechanical complication. One infant in the long-term group developed an arrhythmia (blocked atrial bigeminy after a PCVC had been in place for 6 days). The infant was started on digoxin. Results of an echocardiogram were normal. The arrhythmia was not believed to be related to the central catheter placement, and the catheter was not removed or adjusted. No subject suffered embolus, hemorrhage, pleural effusion, or a broken catheter.

In the short-term group, 27 (13%) of the 210 total catheters placed by 28 days were removed for mechanical complications, including dislodgment (11 catheters), obstruction (5 catheters), infiltration (8 catheters), leaking (1 catheter), or inability to draw from the catheter (2 catheters). In the long-term group, 27 (15%) of 181 total catheters placed by 28 days were removed for mechanical complications, including dislodgment (14 catheters), obstruction (5 catheters), infiltration (3 catheters), leaking (2 catheters), and inability to draw from the catheter (3 catheters). A higher number of UVCs were removed in the long-term group because the infant had grown and the catheter tip had migrated to a position below the diaphragm despite no change in position at the umbilicus (12 of 113 in short-term group vs 69 of 147 in long-term group).

Other Secondary Outcomes

There were no differences between groups in the number of days to achieve full feedings, days to regain birth weight, or the rate of NEC or death (Table 4). None of the deaths were considered to be related to the study interventions. Neither the number of peripheral blood draws nor the number of peripheral intravenous catheter placements varied between the 2 study groups (data not shown).

Although *Enterococcus*, *Candida glabrata*, *Candida parapsilosis*, and *Malassezia furfur* were listed only as potential pathogens, many experts would consider a single positive culture with these organisms as evidence of

TABLE 4 Outcomes of Central Catheters

	Short-term Group	Long-term Group	P
No. of subjects	106	104	
No. of catheters placed by day 28	1.98 ± 0.63	1.74 ± 0.75	.01
Incidence of catheter infection	14 (13)	21 (20)	.17
Catheter duration at infection, d	11.5 (5–25)	14 (5–28)	.35
Children with thrombi	10 (9)	14 (13)	.36
Children with clinically significant thrombi	4 (4)	7 (7)	.34
Children with pericardial effusions	11 (10)	10 (10)	.85
Incidence of NEC (Bell's ⁴⁰ stage 2 or above)	7 (7)	11 (11)	.30
Days to full feeding	23 (7–101)	22 (7–136)	.84
Days to regain birth weight	9 (0–27)	10 (0–33)	.71
Death	8 (8)	7 (7)	.82

Data are presented as mean ± SD, n (%), or median (range).

infection. If these organisms were reclassified as definite pathogens, 1 additional subject in the long-term group would be categorized as having *C glabrata* infection, resulting in a catheter-associated infection rate of 12.1 per 1000 catheter-days. In no other case was an isolated positive culture obtained for any of these organisms while a catheter was in place during the first 28 days. Other reports have specifically calculated catheter-related infection rates in infants with birth weights ≤1000 g.^{17,20} If the catheter-related infection rates were calculated for study infants with birth weight ≤1000 g, the rates were 8.6 per 1000 catheter-days in the short-term group and 9.2 per 1000 catheter-days in the long-term group.

In the short-term group, 13 subjects deviated from the protocol by having PCVCs placed after 10 days. In the long-term group, 2 subjects had UVCs left in place past 28 days, resulting in protocol deviation. Although not expressly prohibited by the protocol, 1 short-term subject and 20 long-term subjects had a UVC replaced with another UVC after 7 days of age. Five (24%) of these infants (1 short-term subject and 4 long-term subjects) developed infection while a late-replaced catheter was in place.

One-Year Follow-up

To date, 180 of 210 study subjects (15 deceased, 15 lost to follow-up) have returned information regarding 1-year follow-up. Only 1 child, who was in the long-term group, had liver disease (cholestatic hepatitis, with no evidence of portal hypertension). This child subsequently underwent a follow-up echocardiogram, the results of which were normal.

DISCUSSION

Long-term use of a UVC did not result in fewer catheter-related infections than short-term use of a UVC followed by use of a PCVC. The incidences of catheter-related thrombi and other complications did not differ between groups, although the majority of catheter-related thrombi occurred at the site of the UVC tip. Long-term

use of a UVC resulted in a lower total number of catheters being placed than short-term use of a UVC followed by use of a PCVC.

The limited data available after 14 days in this trial suggest the possibility of increased infection in the long-term group. The apparent 7% absolute difference in infection rates between the short-term and long-term groups, although not statistically significant, would have potential clinical significance if it were to be substantiated. Although our trial had 80% power to detect a difference in absolute risk of 16% (11% vs 27%) between the 2 study arms, it remains true that relatively small (but real) group differences cannot be ruled out by this study. The 7% risk difference between the groups in our trial had 95% confidence limits of –3% and 17%. A larger, multicenter study with a power of at least 90% would be needed to conclude definitely that there were no differences in the infection and complication rates between long-term UVCs and short-term UVCs, particularly in the period between 14 and 28 days.

Several studies have evaluated infection rates after umbilical catheterization.^{15,17,21–23} The incidence of catheter colonization, defined by either catheter-tip culture or the presence of organisms in a blood culture in the absence of clinical symptoms, has been estimated at 39% to 100% for catheters left in place for 1 to >6 days.^{15,21–23} Some studies have suggested an increasing incidence of colonization with increasing catheter dwell time,²¹ whereas others have suggested very early colonization (<24 hours),²³ with no effect of increasing dwell time on colonization incidence.^{22,23} The incidence of UVC colonization seems not to differ from the incidence of colonization of peripheral intravenous catheters.²¹ The incidence of catheter-related infection (positive culture with symptoms or treatment) has been estimated at 6% in UVCs left in place for ≥3 days¹⁵ and 24% to 27% among UVCs left in place for up to 14 days.¹⁴

Infection of PCVCs has also become a major concern in neonates.^{8–13} Trotter¹³ conducted an integrated literature review to determine the rate of sepsis in neonates with PCVCs. Trotter found that catheter-related sepsis

occurred in 0% to 29% of catheters, resulting in 0 to 15.3 infections per 1000 catheter-days.¹³ PCVC-related infection incidences ranging from 17% to 31%, with rates as high as 22 per 1000 catheter-days, have been reported in subsequent studies.^{12,24} Mean (or median) age at infection ranged from 12.5 to 19.7 days, and length of catheter dwell was not related to risk of infection.^{24,25}

The incidence of catheter-related infection among infants in our study who had long-term use of UVCs (20%) is congruent both with the infection rates reported for PCVC use in other studies and for UVC use up to 14 days. As reported in several other studies, the infection rate in long-term UVCs did not seem to accelerate over time.^{22,23} The infection rate of 11.5 per 1000 catheter-days in the long-term group is also consistent with data reported by the National Nosocomial Surveillance System, which indicated that pooled mean umbilical catheter and central venous catheter-associated bloodstream-infection rates for NICUs ranged from 3.5 to 3.8 per 1000 catheter-days in children whose birth weight was >2500 g to 9.1 to 11.3 per 1000 catheter-days in children with birth weight ≤1000 g.^{17,20} Indeed, if only infants of ≤1000 g birth weight are considered, both groups in our study were comparable to the lower pooled-mean estimate.

Mechanical complications of central venous catheters are also quite common.²⁶ Studies of PCVCs have reported the incidence of mechanical complications (including dislodgment, extravasation, occlusion, phlebitis, and pleural effusion) necessitating removal to be between 26% and 39%.^{12,27} Compared with previously reported rates, a relatively small proportion of our catheters (14% overall) required removal for mechanical reasons, and this rate did not vary between groups.

Infants with central catheters are not routinely screened for clot formation, and as a result, the incidence and significance of clinically unsuspected thrombi are unknown. Kitterman et al² reported that the incidence of catheter-related thrombosis in infants with UVCs varied from 3% to 33% as determined by autopsy studies and follow-up examination of surviving infants. A small case-control study (31 infants per group) suggested that 26% of infants with UVC tips lying in the left atrium would have echocardiographically detectable thrombus, whereas 3% of those with UVC tips below the left atrium would have thrombus.⁷ Symptomatic thrombosis, however, remains a relatively rare event in NICUs, with reported incidences of 5.1 per 100 000 live births and 2.4 per 1000 NICU admissions.^{28,29}

In our study, blinding clinical caregivers to all echocardiogram results could have caused them to miss clots that were clinically significant, whereas revealing all echocardiogram results could have caused them to discontinue central catheters for clots that were clinically insignificant. This led to our decision to report only

thrombi that were deemed clinically significant by the study cardiologist. Our rate of thrombus detection (10% overall) is higher than most rates determined by passive collection and significantly higher than the rate of symptomatic thrombi. The rate of thrombus acquisition did not accelerate over time and did not seem to be higher in infants who had UVCs in place for up to 28 days. Although mortality has been reported from catheter thrombi,³⁰ none of the thrombi in our subjects were treated, and all resolved spontaneously. The elevated incidence of catheter thrombosis that we observed in SGA infants is consistent with other reports of increased thrombogenic potential in SGA infants, perhaps because of polycythemia or abnormalities of the coagulation cascade.³¹ Portal hypertension is an infrequently encountered late complication of umbilical vein catheterization that is felt to be related to portal venous thrombosis.⁴ The planned 5-year follow-up for children in our study will be crucial to determine any long-term complications.

Although pericardial and pleural effusions can be catastrophic complications of central venous catheters in newborns,^{6,32-36} no significant pleural or pericardial effusions were detected in our study among infants with a catheter in place. Small pericardial effusions in our study subjects were as likely to be seen when no catheter was in place as with a catheter present and, in many cases, might have been unrelated to the catheters. We recognize that our study group may be too small to have detected rare, serious complications such as large effusions. Reports based on several thousand catheters have suggested incidences of symptomatic pericardial effusion ranging from 0.5 to 1.8 symptomatic effusions per 1000 PCVCs, although other, smaller reports of single-unit experiences have reported symptomatic effusion rates up to 3%.^{33,35,37} The incidence of trivial pericardial effusion on routine echocardiography has not been directly described, but isolated pericardial effusion in the absence of associated pathology is a recognized finding on fetal echocardiography.³⁸

To date, there are limited data comparing the risks and complications of UVCs versus PCVCs. A recent prospective study of 67 infants found that those who had UVCs remaining in place for up to 14 days had no increase in rates of sepsis or complications when compared with those who had been randomly assigned to have no UVC in place. There was no specified protocol for achieving intravenous access in infants in the no-UVC group. During the first week of life, 53% of infants in the no-UVC group had PCVC-placement attempts, whereas no PCVC-placement attempts occurred in the UVC group. The overall successful catheter-placement rate was 70% for UVCs and 46% for PCVCs. The proportions of subjects in each group with sepsis, defined as positive blood culture and >3 days of antibiotic treatment, were similar (no-UVC group: 25%; single-lumen UVC: 27%; double-lumen UVC: 24%). Interpretation of

the results was complicated by a large number of subjects who unexpectedly withdrew from the study (56 of an initial 123 enrollees). However, the authors concluded that using a UVC during the first 2 weeks of life is a relatively safe, less stressful, cost-effective means of providing intravenous therapy to neonates.¹⁴

Our study has several technical limitations. Although echocardiograms were performed on UVCs and PCVCs, it may be more difficult to detect thrombi on the tips of PCVCs because of their location in vessels, often farther removed from the heart. Even intracardiac UVC-related thrombi can be difficult to detect by echocardiography.³⁹ Given these factors, we are likely to have underestimated the number of clots present on PCVCs.

There was also a potential ascertainment bias toward detection of infection in the long-term group. It is often difficult to draw blood from small-bore PCVCs. Of the 8 isolated positive cultures (6 in the short-term group, 2 in the long-term group) for nonpathogens obtained while a PCVC was in place, a paired central culture could be drawn in only 4 instances (3 in the short-term group, 1 in the long-term group). In contrast, of the 10 isolated positive cultures (2 in the short-term group, 8 in the long-term group) for a nonpathogen obtained while a UVC was in place, 8 of 10 (1 in the short-term group, 7 in the long-term group) had simultaneous central cultures drawn. The incidence of catheter infection in PCVCs, and consequently in the short-term group, may have been underestimated. However, if true, this finding would only strengthen our conclusion that long-term use of UVCs did not present an increased risk of infection in comparison to the short-term use of a UVC followed by use of a PCVC.

CONCLUSIONS

Long-term use of UVCs up to 28 days seemed to neither increase nor decrease infection and other risks when compared with short-term use of a UVC followed by placement of a PCVC. Our data support the Centers for Disease Control and Prevention recommendation that UVCs may be left in place for up to 14 days. Although fewer subjects with UVCs remained between 14 and 28 days, continuation beyond the current recommended limit may also be reasonable. Additional studies with higher power to evaluate the safety of more prolonged UVC placement would be justified.

ACKNOWLEDGMENTS

This research was supported in part by grant 5 M01 RR00044 from the National Center for Research Resources (National Institutes of Health, Bethesda, MD) for the University of Rochester General Clinical Research Center and by a Strong Memorial Hospital Innovations in Patient Care grant.

We thank Drs Dale Phelps, Roger Vermilion, and Mary Caserta for service on the Data and Safety Moni-

toring Board. We also thank the University of Rochester Neonatal Clinical Trials Group for intellectual input; Drs Dwight Hardy and Geoffrey Weinberg for bacteriologic expertise; Dr Timothy Stevens for critical reading of the manuscript; the NICU staff for their participation; and the subjects' parents for their generosity.

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A Randomized Trial Comparing Long-term and Short-term Use of Umbilical Venous Catheters in Premature Infants With Birth Weights of Less Than 1251 Grams

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Pediatrics 2006;118:e25-e35; originally published online Jun 19, 2006;

DOI: 10.1542/peds.2005-1880

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