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Safety of Central Venous Catheter Placement at Diagnosis of Acute Lymphoblastic Leukemia in Children

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Abstract

Background—Central venous catheters (CVC) facilitate the management of patients with cancer. Optimal timing for placement of a CVC is controversial. We sought to determine whether early placement in children with acute lymphoblastic leukemia (ALL), a group at high risk for infection and thrombosis, was associated with an increased rate of surgical complications.

Procedure—We evaluated the incidence and risk factors for early surgical complications in children with ALL diagnosed between 2004 and 2009 at a single pediatric cancer center.

Results—One hundred seventy-two patients were studied. There were 17 episodes of bloodstream infection, for a 30-day incidence of 9.8% (95% CI, 5.9–15%). There were no surgical site infections and no CVC was removed due to infection. Early thrombosis occurred in only one patient, 3 days after CVC placement. Infection was not influenced by catheter type, patient age, body mass index, or fever at the time of placement. The infection rate was not statistically higher when the ANC was <500/mm^3 at the time of CVC placement (14.2% vs. 6.8%; $P = 0.12$).

Conclusion—Early CVC placement at the time of diagnosis of ALL was associated with a low surgical complication rate with no catheters requiring removal due to infection. Utilizing our current methods of preoperative preparation, surgical management and postoperative CVC care, early placement of a CVC is safe in children with ALL even when their ANC is <500/mm^3, but larger cohort studies would be helpful to further clarify this issue. Pediatr Blood Cancer 2012;58:498–502.

Keywords

children; infection; leukemia; neutropenia; pediatric

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INTRODUCTION

Indwelling central venous catheters (CVC) facilitate the management of children with malignancies, but their use is associated with various adverse events (infectious and mechanical complications) in a proportion of patients [1]. This has been documented in solid cancer and leukemia patients; however, the optimal timing for placement of a CVC is controversial. Infection is the most frequent complication of indwelling catheters, with a reported incidence of "early infection" (i.e., infections occurring within the first 30 days after CVC insertion) ranging from 8% to 22% [2,3]. Mechanical catheter-related complications (catheter breakage, occlusion, catheter migration into the right atrium, accidental CVC self-removal) are variable ranging from 4% to 20% [4,5], and thrombosis occurs with a reported incidence of 3.3–10% [6,7].

The aim of the present study was to assess the safety of early catheter placement in children with newly diagnosed acute lymphoblastic leukemia (ALL) and to identify risk factors associated with catheter complications, in a single pediatric cancer center.

PATIENTS AND METHODS

Patients

After receiving Institutional Review Board approval, we reviewed the medical records of 172 children with newly diagnosed ALL who had indwelling catheters, externalized tunneled, or totally implantable devices inserted within 5 days of diagnosis between December 2004 and January 2009 at St. Jude Children's Research Hospital. Patients received similar remission induction chemotherapy, including prednisone, vincristine, L-asparaginase, daunorubicin, and intrathecal therapy. During the study period, three different types of indwelling CVCs were inserted: double lumen tunneled catheters (DLTC), single lumen tunneled catheters (SLTC), and totally implantable access ports (infusaport). The choice of catheter was based on patient or parent preference, the absolute neutrophil count (ANC) at the time of insertion (generally using tunneled catheters (TC) for patients with ANC < 500/mm^3), possible need of bone marrow transplant in the management of high-risk leukemia (typically using a DLTC) and age (generally using TC in patients younger than 5 years). The size of the catheter was determined by the weight of the patient, preferring 6.6 or 7 French catheters in patients <30 kg.

CVC Placement and Postoperative Maintenance

All patients were evaluated prior to the surgical procedure. Patients with hemoglobin below 8 g/dl or platelets below 50,000/μl received blood products prior to the surgical procedure. An absolute contraindication for CVC placement under general anesthesia was the presence of a large mediastinal mass with airway compression. In those patients a peripherally inserted central catheter (PICC) was placed under local anesthesia and CVC insertion deferred. All surgical procedures were performed with sterile technique in the operating room. Antibiotic prophylaxis was administered to all patients. Intravenous cefuroxime 50 mg/kg was administered preoperatively and two doses of 10 mg/kg were administered orally every 12 hours after the procedure. Clindamycin was substituted preoperatively, using a

similar schedule, if the patient was allergic to penicillin or cephalosporin and was not receiving other antibiotic treatment at the time of the catheter placement. Patients receiving broad-spectrum antibiotic treatment prior to the surgery were maintained with the same treatment until defervescence and documentation of negative cultures.

All catheters were placed using a percutaneous method under general anesthesia. Central venous catheter insertion was performed by cannulating the subclavian vein using an infracla-vicular percutaneous approach. Correct position was confirmed using fluoroscopy during the procedure and a standard chest radiograph was obtained immediately after the procedure.

Postoperative CVC care and maintenance procedures were performed according to the nursing policy and procedure manual of our institution. While not in use, TC were flushed daily by nurses or trained parents using a heparinized solution (10 units/ml) containing the preservative parabens [8]; infusaports were flushed at least monthly by trained nurses with a similar solution but with a heparin concentration of 100 units/ml. The exit site dressing was changed three times per week for external TC. The exit site was cleaned with 2% chlorhexidine or povidone iodine if the patient was allergic to chlorhexidine, or <2 months of age. The catheter was cleaned with alcohol from the exit site to the end of the CVC and the sterile occlusive dressing was applied again. While in use, the huber needle in the infusaport was changed weekly.

Data Collection

Medical records of all newly diagnosed children with ALL who received a permanent central catheter were reviewed; we recorded age, body mass index (BMI), history of a previous central catheter placement, documented preoperative infection, presence of fever within 24 hours and positive cultures before catheter placement, white blood count (WBC), ANC, platelet count, hemoglobin, and glucose at the time of the CVC insertion. The date of placement, date of initiation of chemotherapy, catheter type and size, site of insertion, surgical complications, and infectious complications were recorded [9], including bacteremia, sepsis, exit site infection, tunnel tract infection, infusaport pocket infection, and skin infection within 30 days of CVC insertion. We also recorded all mechanical complications and episodes of symptomatic thrombosis during the same interval.

Infectious complications were defined as follows: (1) bacteremia—defined as isolation of a pathogen from a blood culture drawn through the catheter [10–12]; (2) exit site infection—defined by the presence of erythema, induration, and tenderness within 2 cm of the exit site; (3) tunnel tract infection—defined as induration, erythema, tenderness, and edema >2 cm from the exit site or evidence of pus, along the tunnel of the CVL; (4) sepsis—defined by the presence of catheter-associated bacteremia associated with tachycardia and/or tachypnea; (5) septic shock—defined as the presence of sepsis and cardiovascular organ dysfunction, (6) infusaport pocket infection—defined as erythema, induration, and tenderness within 2 cm of the infusaport; and (7) skin infection—erythema, induration, and tenderness or evidence of pus at the surgical incision.

Febrile patients were evaluated clinically and blood cultures were obtained from the central venous catheter and in most cases also by peripheral venipuncture. Patients were admitted to the hospital and started on broad spectrum antibiotics. In patients with bacteremia, sepsis and septic shock, antibiotic coverage was adjusted to organism sensitivity; the patients were treated for 10–14 days until resolution of the clinical symptoms and negative blood cultures.

Mechanical complications included dislodgment of the CVC tip into a smaller vessel (e.g., internal jugular), accidental CVC self-removal, blockage, breakage, or occlusion. Occlusion was defined as difficulty drawing blood and/or infusing solutions through the CVC that could not be alleviated by positional changes or heparin flushes, requiring local instillation of a thrombolytic agent to reestablish the ability to draw blood through and to flush the catheter easily [13]. Thrombosis was confirmed with Doppler ultrasound or venogram in patients who presented with pain, swelling, and discoloration of the upper extremities or withdrawal occlusion.

Statistical Analysis

The incidence rates of complications within 30 days were estimated with associated 95% confidence intervals (CIs) using the Blyth–Still–Casella method [14].

The probability of CVC complication over time was determined from the date of insertion to the date of complication or to 30 days if no complication occurs and estimated using Kaplan–Meier method [15].

To detect 10% difference (80% power and 5% type I error) of infection rates versus different risk factors we needed 160 patients/per group, this study has a cohort of 172 patients, and a limited number of complications, therefore univariate Cox-regression was used to study the associations between early infection and potential risk factors.

Results are reported as hazard ratios (HR) with associated 95% CIs and *P*-values; a *P*-value <0.05 was considered statistically significant.

For each device, the total number of days at risk was calculated as the number of days from insertion to the last follow-up: 30 days after insertion or day of removal. The rate of catheter-related infectious complications per 1,000 days was calculated as 1,000 times the number of infections divided by the total number of catheter-days at risk, and reported with their 95% CI using the bootstrap percentile method [16].

RESULTS

Patients

Characteristics of the 172 patients who met the study criteria are summarized in Table I. One of 172 patients (0.58%) had his CVC removed 5 days after insertion because of a kink between the hub of the infusaport and the distal catheter. There were no other catheters removed during the 30-day study interval; hence, the 171 remaining catheters were followed for 30 days, resulting in a total of 5,135 at risk catheters-days.

Infectious Complications

There were 17 infectious episodes (14 bacteremia and 3 septic shocks) diagnosed at a median of 13 days after catheter placement (range, 8–26 days); no infections occurred within the first week after catheter placement. Analysis of the infectious episodes using time-to-detection criteria [10–12] for definition of CVC-related infection, only 1 patient was clearly define as catheter-related infection, 11 were indeterminate, and 5 non-catheter related, for statistical purposes we defined all infectious episodes. Therefore, the rate of early catheter-related infections among the study population was 9.8% (95% CI, 5.9–15%) with an overall rate of 3.31 episodes/1,000 catheter-days (95% CI, 1.63–4.23) during the 30-day observation period. There were no recurrent bloodstream infections. There were no surgical wound, exit site, pocket, or tunnel tract infections. Details of the infectious complications are provided in Table II.

Cox-regression analysis showed that none of the potential risk factors was associated with CVC infection (Table III). The mean ANC at insertion for all patients was 600/mm^3 (range 0–40,885/mm^3). Patients with ANC <500/mm^3 at the time of insertion did not have statistically significant higher incidence of infection (14% [95% CI, 7.1–25%] vs. 6.8% for those with an ANC > 500/mm^3 [95% CI, 3.3–13%]; $P = 0.12$). All 17 patients with early catheter-related infection in our study had an ANC < 100/mm^3 at the time of their infection.

Mechanical Complication

There were four mechanical complications in our study group. In three cases, the tip of the catheter became malpositioned, two of these were repositioned with high-pressure flush of the CVC with saline solution, and one was repositioned with an endovascular procedure. One infusaport was removed and replaced in a different site because dysfunction resulted from the development of a kink between the catheter and the hub. Occlusion occurred in 21 of 172 patients (12%) and resolved in all cases after infusion of a thrombolytic agent. The infection rate was not statistically greater in patients in whom withdrawal occlusion occurred (19% vs. 8.6%, RR 2.47, 95% CI, 0.81–7.58; $P = 0.11$).

Thrombosis

One episode of thrombosis was diagnosed 3 days after the catheter placement, when upper extremity swelling was noted and thrombosis was confirmed by angiogram; the patient was treated with systemic anticoagulation, with resolution of thrombosis after 4 days of treatment and without removal of the CVC.

DISCUSSION

While the optimum time for placement of CVL remains controversial in the ALL patient early bloodstream infection, although the most frequent catheter-related complication, was relatively low (17 episodes—infection rate 3.31 episodes/1,000 CVC-days—with only one episode being definitely considered as catheter-related) in this study. Mechanical complications occurred in four cases and early thrombosis was recorded in only one patient. We did not find a statistically increased risk of infection in patients who had ANC was <500/mm^3 at the time of CVC placement (14.2% vs. 6.8%; $P = 0.12$), but this difference

was not statistically significant. No CVC was removed due to early infection, and only one infusaport was removed and replaced because of malfunction. Infection, was not influenced by, patient's age, BMI, or fever at the time of placement. The relatively low rate of infection in our population may be in part due to our routine use of antibiotic prophylaxis, and the strict observance of the nursing guidelines in the care and maintenance of the CVC. The same devices and operative procedure remained constant during the period of the study.

The use of intraoperative antibiotic prophylaxis can reduce the incidence of early infection [17], and so all of our patients received perioperative antibiotics. Patients with fever or positive cultures before the placement of the CVC continued to receive broad spectrum antibiotics and patients not treated with antibiotics, received intraoperative cefuroxime or clindamycin prior to the surgery.

Although infection control guidelines classify infections occurring in the first 30 days after catheter-placement as surgical complications, in many instances, these infections are likely not related to the surgical procedure. Bacteremia is common throughout cancer therapy, even months after CVC placement, and so bacteremia cannot be definitively attributed to CVC placement, particularly when it occurs a week or more afterwards. In fact, using time-to-detection criteria and comparison to the results of peripheral blood cultures [10–12], only 1 of the 17 bacteremias or sepsis in this study was definitively classified as catheter-related, while 5 were not catheter-related and 11 were indeterminate (Table II).

Previous studies have shown a high rate of catheter-related infection in patients with neutropenia at the time of the catheter insertion. Penel et al. [17] reported that neutropenia, defined as an ANC < 500/mm^3, at the time of insertion is a risk factor for CVC-related infections. We did not find a statistically increased risk of infection in patients who were neutropenic at the time of catheter placement (14.2% vs. 6.8%; $P = 0.12$). Other authors had also shown that an ANC <500/mm^3 on the day of CV insertion is not a risk factor [18].

Many practitioners consider preoperative fever to be a relative contraindication for the placement of long-term catheters, despite a dearth of data demonstrating fever as a significant risk factor [17]. In our practice, when fever is present prior to the placement of the indwelling CVC, blood cultures are drawn and broad-spectrum empiric antibiotic coverage is initiated. Antibiotics are discontinued when the patient becomes afebrile, is without clinical symptoms and has negative blood cultures. With this approach, the presence of fever at the time of catheter insertion was not a risk factor for the development of catheter-related infection in this study.

Previous reports have shown the type of catheter to impact the incidence of infectious, mechanical complications, and thrombosis [5,19]. It has been our preference to place tunneled catheters (SLTC or DLTC) rather than infusaports in patients with ANC < 500/mm^3 at the time of surgery [20]. Notably, all infections in this study occurred late after CVC insertion (8 days or more) and no surgical wound infections were seen. Future studies need to address the safety of placement of a totally implanted catheter in the presence of neutropenia.

Catheter removal was never required to clear an infection in this study. The successful management of bacteremias in our patients may be a reflection of our strategy to start antibiotic treatment in all patients with febrile episodes and deliver antibiotics through the lumen of the CVC and using antibiotic lock therapy when indicated [21].

There were no major mechanical complications or thrombosis episodes. Catheter occlusion has been reported in up to 25% of all catheters [13,22], and was found to be especially high in patients with ALL during remission induction chemotherapy due to the concomitant use of L-asparaginase and steroids [23]; however, in our series this complication was present in only 12.2% of the patients. In all patients occlusion resolved with infusion of thrombolytics. An association between occlusion and thrombosis with the presence of infection has been described [22]. Thrombus formation produced by the presence of a fibrin sheath in the inner surface of the catheter can lead to adherence of various bacteria, especially *Staphylococcus aureus* and certain gram negative bacteria [24]. The association between infection and occlusion did occur in our patient population but is not statistically significant ($P = 0.11$), possibly because of the small sample size and low incidence of infection.

Our policy has been to place a CVC at the time of diagnosis of ALL. Following our current protocols of careful preoperative evaluation, standard surgical techniques, and meticulous postoperative CVC care, we had a low incidence of major catheter-related complications, a low rate of infections and a low rate of catheter removal [25]. The study has the limitations of a retrospective, non-randomized, non-observational study; however, the results supports our present recommendation that long-term CVC placement is safe in children with newly diagnosed ALL. With our current infection rates a larger cohort (160 patients/per group) is needed to detect 10% difference between different risk factors (80% power and 5% type I error). Future studies need to address the safety of placement of a totally implanted catheter in the presence of neutropenia.

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TABLE I

Characteristics of the Study Population (172 Patients)

Characteristic	N (%)
Age at therapy initiation	
Median	4 years
Range	4 days–16 years
Sex	
Male	97 (56%)
Female	75 (44%)
Body mass index	
Median	16
Range	10–33
Febrile during the 24 hours prior to CVC placement	
No	126 (73.3%)
Yes	46 (26.7%)
Positive cultures prior to CVC placement	
No	166 (96.5%)
Yes	6 (3.5%)
Presence of previous non-permanent CVC	
No	165 (95.9%)
Yes	7 (4.1%)
Day of treatment at the time of CVC placement	
Median	0
Range	−1 to 5
Type of catheter	
Double lumen tunneled catheter	7 (4.1%)
Single lumen tunneled catheter	132 (76.7%)
Infusaport	33 (19.2%)
White blood count at placement	
Median	5,800/mm^3
Range	184–314,500/mm^3
Absolute neutrophil count at placement	
Median	600/mm^3
Range	0–40,888/mm^3
<500/mm^3	102 (59.3%)
>500/mm^3	70 (40.7%)
Platelet count at placement	
Median	110,000/μl
Range	43,000–447,000/μl
Hemoglobin at placement (posttransfusion)	
Median	9.1 g/dl
Range	6.2–14.6 g/dl

CVC, central venous catheter.

TABLE II

Characteristics of 17 Patients With Bacteremia, Sepsis, or Septic Shock

Gender	Age	WBC at placement (/mm^3)	ANC at placement (/mm^3)	BMI	Type of catheter	Infection	Day of infection	ANC at infection (/mm^3)	Organism	CVC-related infection using time-to-detection criteria
F	2 years	19,300	300	20	SLTC	Bacteremia	8	0	*Pseudomonas aeruginosa*	Indeterminate
M	15 years	4,300	200	21	SLTC	Bacteremia	9	100	*Staphylococcus aureus*	Indeterminate
M	10 days	1,700	700	15	SLTC	Bacteremia	10	0	Coagulase neg staphylococcus	Indeterminate
F	2 years	5,900	177	20	SLTC	Bacteremia	11	0	Viridans streptococcus	Not catheter-related
M	3 years	60,000	3,900	15	SLTC	Bacteremia	11	0	*Streptococcus mitis*	Indeterminate
M	9 years	4,300	100	20	TIAP[a]	Bacteremia	12	0	*Acinetobacter baumannii*	Indeterminate
F	3 years	4,400	400	18	SLTC	Septic shock	12	100	*Pseudomonas aeruginosa*	Indeterminate
F	3 years	43,500	500	16	SLTC	Sepsis	13	0	*Bacillus cereus*	Not catheter-related
M	3 years	2,500	0	15	SLTC	Bacteremia	13	0	*Pseudomonas aeruginosa*	Not catheter-related
F	2 years	8,500	200	15	SLTC	Bacteremia	14	0	*Klebsiella pneumoniae*	Not catheter-related
M	15 years	8,600	100	33	SLTC	Septic shock	15	0	*Escherichia coli*	Catheter-related
F	2 years	41,600	700	17	SLTC	Bacteremia	16	0	*Neisseria cineria*	Indeterminate
F	14 years	98,000	1,500	22	TIAP[a]	Bacteremia	17	0	*Escherichia coli*	Indeterminate
F	2 years	6,300	900	13	SLTC	Bacteremia	17	100	*Streptococcus sanguis*	Indeterminate
M	12 years	3,300	500	14	SLTC	Septic shock	19	100	*Staphylococcus aureus*	Not catheter-related
F	3 years	8,400	168	24	SLTC	Bacteremia	25	0	*Pseudomonas aeruginosa*	Indeterminate
M	12 years	1,700	400	32	SLTC	Bacteremia	26	0	Coagulase neg staphyloccocus	Indeterminate

SLTC, single lumen tunneled catheters; CVC, central venous catheter.

[a]Infusaport.

TABLE III

Cox-Regression Analysis of Potential Risk Factors for Infection Associated With Central Venous Catheter Placement

	Infection			
Risk factor	**No**	**Yes**	**Hazard ratio (95% CI)**	***P*-value**
Body mass index				
<25	148	15		
≥25	7	2	2.4 (0.5–10.5)	0.24
ANC at placement (/mm^3)				
<500	60	10	0.4 (0.2–1.2)	0.11
≥500	95	7		
Febrile during last 24 hours				
No	111	15	0.3 (0.1–1.5)	0.17
Yes	44	2		
Positive culture prior to surgery				
No	149	17	NA	NA
Yes	6	0		
Value of Glucose (g/dl)	Median	97		
	Range	11–245	0.9 (0.9–1.0)	0.57
Age (years)	Median	4		
	Range	0.01–16.2	1.0 (0.9–1.1)	0.39
Body mass index	Median	16		
	Range	10–33	1.0 (0.9–1.1)	0.53
ANC at placement (/mm^3)	Median	600		
	Range	0–40,885	1.0 (0.9–1.0)	0.15
Withdraw occlusion				
No	138	13	2.4 (0.8–7.5)	0.11
Yes	17	4		
Number of CVC lumen				
Single lumen	148	17	NA	NA
Double lumen	7	0		
Vein used				
Left subclavian vein	104	12	0.8 (0.3–2.4)	0.76
Right subclavian vein	51	5		

CNC, central venous catheter; NA, not applicable; ANC, absolute neutrophil count.