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A prospective survey on incidence and outcome of Broviac/Hickman catheter-related complications in pediatric patients affected by hematological and oncological diseases

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Abstract A prospective pediatric survey on the incidence of central venous catheter (CVC) complications was performed aimed at identifying risk factors of premature CVC removal. The study comprised 129 Broviac-Hickman CVCs inserted during a 13-month period in 112 children. The total number of CVC days was 19,328 (median: 122 days, range: 1–385). The overall rate of complications was 6.2/1000 CVC days, i.e., 4.5/1000 and 1.7/1000 CVC days for mechanical and infectious complications, respectively. Interestingly, only two CVC-related cases of septicemia and no thrombotic events were documented. At the end of the study period, 38 of 129 CVC (29.5%) had been removed: 20 due to CVC-related complications (dislocation18, rupture 2), 10 due to the patient's death, and 8 due to completion of therapy. Age at CVC insertion <4.9 years was a significant predictor of premature CVC removal (p=0.01). Mechanical complications, especially in younger children, are the main cause of premature loss of CVC. These data underline the importance of more effectively securing the CVC to subcutaneous tissue in pediatric patients to reduce accidental dislocations.

Keywords Broviac/Hickman central venous catheter · Complications · Infections · Pediatric malignancy

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Introduction

The central venous catheter (CVC) is an essential tool in the management of pediatric hematology-oncology patients as it provides a durable and atraumatic venous access for blood sampling and the safe administration of cytotoxic drugs, intravenous drugs, blood components, and parenteral nutrition [1].

The potential drawbacks of indwelling catheters are several complications such as local or systemic infection (skin infections at the exit site, tunnel infections, catheter-related sepsis), mechanical complications (dislocation or rupture, malfunction due to the formation of clots within the lumen or at the catheter tip), and deep venous thrombosis. It has been estimated that the incidence of CVC-related bacteremia is 2.5 episodes/1000 CVC days and that the incidence of thrombotic complications varies from to 1 to 75% of CVCs depending on the diagnostic technique used [2]. In some instances, these complications are life threatening or require the premature removal of the CVC [3, 4].

Optimal CVC management requires properly trained personnel and adequate guidelines for routine maintenance (flushing of the lumen, exit site dressing) and for dealing with CVC-related complications [5, 6, 7, 8]. Compliance with these guidelines may vary at different centers and should be periodically monitored by specific surveillance programs.

This study describes a prospective survey on the incidence of CVC complications in a pediatric hematology oncology center and focuses on the risk factors for premature CVC removal.

Patients and methods

The study comprised all Broviac-Hickman CVCs inserted at our center between 1 January 2000 and 31 January 2001. Indications for inserting a CVC were the need to administer intensive and/or high-dose chemotherapy, supportive measures (frequent transfusions of blood products, parenteral nutrition), and hematopoietic stem cell transplantation. A single-lumen CVC was inserted at diagnosis in patients with standard-risk malignancies who were candidates only for chemotherapy, while a two-lumen CVC was inserted in all patients, at diagnosis or relapse, whose treatment plan required autologous or allogeneic peripheral or blood hematopoietic stem cell transplantation, such as high-risk leukemia and lymphoma, metastatic solid tumor, and severe aplastic anemia.

All the insertion procedures were performed in the operating room using a surgical or percutaneous approach and taking the utmost sterile barrier precautions under general anesthesia or, in adolescents, with sedation and local anesthesia. Most of the catheters were placed percutaneously using the Seldinger technique. Surgical positioning, obtained by standard cutdown venotomy, was reserved for patients at higher hemorrhagic risk, i.e., unsupported baseline platelet levels of less than 50×10^9/l. The preferred vascular access was the right internal jugular vein or, as a second choice, the right or left subclavian vein. During placement, the correct positioning of the CVC tip at the superior vena cava-right atrium junction was checked by fluoroscopy. At the end of the procedure, the CVC was secured to the CVC exit site with a subcutaneous purse-string suture and to the skin with a silk suture. No systemic antibiotic prophylaxis was routinely given before the procedure or in the 24 h thereafter.

Data regarding patients (age, sex, diagnosis), CVCs (number of lumens, diameter, insertion technique, and cannulated vessel), and early complications were collected on a specific form completed by the surgeon or the anesthetist. Early complications were defined as any complication diagnosed within 24 h of insertion.

Standard routine CVC care was handled by trained pediatric nurses and included flushing the CVC with 3 ml of heparinized solution (heparin, 200 IU/ml) at least twice a week; weekly cleansing with iodopovidone-iodine solution and dressing of the skin at the CVC exit site with sterile gauze. From April to October 2000, a different heparin solution was used since the hospital was supplied with a pre-prepared 5-ml vial at a concentration of 50 IU/ml. Proper aseptic technique and scrupulous hand hygiene were always observed in handling the CVC.

CVC complications were recorded on a specific form by health personnel at the time of diagnosis, when therapeutic procedures were undertaken, and when the results of treatment were evaluated.

Definitions

CVC-related complications were classified as follows: infection, CVC malfunction, mechanical complications, and deep venous or atrial thrombosis and/or pulmonary embolism.

Infections were classified according to published criteria as definite or presumed CVC exit site infection, tunnel infection, and definite, probable, or possible CVC-related bacteremia [6, 9, 10].

CVC malfunction was considered as partial in the case of difficulty to aspirate from or infuse into the CVC, and it was considered complete in the case of inability either to aspirate from or to infuse into the CVC.

Mechanical complications included CVC tip dislocation, rupture, and kinking. CVC dislocation was defined as partial if the Dacron cuff came out of the CVC exit site, but the CVC tip's position was still correct; it was defined as complete if the CVC tip migrated out of the right atrium/superior vena cava junction.

CVC thromboembolic complications included deep venous thrombosis, right atrial thrombosis, and pulmonary embolism.

Management of CVC-related complications

The standard approach to the diagnosis and treatment of CVC-related complications was adopted through medical and nursing protocols that are briefly reported below.

Infection

CVC exit site infection: if local inflammation occurred, a skin swab was submitted to the laboratory; cleansing with iodopovidone-iodine solution and sterile dressing changes were done more frequently, at least every 1–3 days. Empirical antibiotic topical treatment with rifampicin solution was used in the presence of purulence or local inflammation extending more than 1 cm beyond the CVC exit site. The antibiotic treatment was then confirmed, suspended, or adjusted according to the results of the skin swab. If the susceptibility test showed rifampicin resistance, topical application of teicoplanin was used. The exit site infection was monitored visually and microbiologically (if positive, initially) until resolution or for at least 7 days before deciding on CVC removal. No systemic antibiotic treatment was administered if the patient was without fever.

Tunnel infection: when the clinical diagnosis was made, a CVC exit site skin swab and CVC blood culture were taken and antibiotic treatment was promptly started with teicoplanin at a dose of 10 mg/kg/day (maximum dose 400 mg/day). If the patient was feverish, a third-generation cephalosporin and/or amikacin was associated (see below). In the event of a positive culture, the treatment was adjusted according to the susceptibility test and continued for at least 3 days before deciding whether to remove the CVC or until resolution.

Definite, probable, or possible CVC-related bacteremia: patients with fever were promptly treated with an empirical association of teicoplanin and a third-generation cephalosporin (mainly ceftazidime) [11]; amikacin was added in the case of severe neutropenia [polymorphonuclear cells (PMN) $<0.5\times10^9$/l] [12]. Adjustments were made, if necessary, according to the susceptibility test on the germs isolated by the blood culture. The treatment was continued until resolution or for at least 3 days before deciding whether to remove the CVC. If the patient's temperature returned to normal, flushing of the CVC induced no chills, and at least two consecutive blood cultures drawn from the CVC were negative, any CVC-related infection was considered to be resolved. Antibiotics were administered by brief i.v. infusion after dilution with 50 ml 5% dextrose solution. No continual infusion or lock techniques were used.

Mechanical complications: the most common signs were inability to draw through and/or infuse into the CVC. The diagnostic evaluation was based on the visual and manual assessment of the position of the Dacron cuff and a chest X-ray to rule out CVC dislocation or kinking.

If pain or swelling was noted along the subcutaneous CVC tract during infusion of any solution or at CVC flushing, fluoroscopy was performed with the injection of an enhancement medium to diagnose any CVC ruptures.

Once mechanical complications had been ruled out, CVC malfunction was assumed to be related to blood component aggregates on the inside of the CVC or to the development of a thrombus around the CVC's tip. Treatment was based on one or two administration(s) of 5000–10,000 IU of urokinase, left in the CVC lumen for 2 h [7, 13]. Sudden occurrences of CVC malfunction during or immediately after the infusion of drugs, blood components, or parenteral nutrition were considered due to the precipitation of crystals or the formation of microaggregates among the infused components. In these cases, alcohol or hydrochloric acid

was used, as reported elsewhere [14]. If urokinase and/or alcohol or hydrochloric acid failed to restore CVC patency, the CVC was removed. Rupture of the external tract of the CVC was repaired, wherever possible; otherwise the CVC was removed, as it was for rupture of the internal portion of the CVC.

CVC-related thrombosis: when suggested by clinical symptoms, color Doppler ultrasound was used for the noninvasive diagnosis of CVC-related thrombosis [15]. Treatment was based on published guidelines for antithrombotic therapy in pediatric patients [8].

Statistical analysis

All data were entered prospectively in a database and analyzed at the end of the study period. The complications were calculated per CVC and/or per 1000 days of CVC life, respectively. The statistical method used to compare proportions and medians of continuous data were the χ^2 and Fisher's exact tests, respectively. The role of sex (M vs F), median age at CVC positioning, underlying disease (diagnosis of leukemia and lymphoma vs other diagnoses), CVC positioning method (percutaneous vs surgical), number of CVC lumens (1 vs 2), type of cannulated vessel (subclavian vein vs others), and diameter of CVC (>7 French vs <) in determining the premature removal of CVC was explored by univariate analysis. A p value of 0.05 was considered significant. Factors with a p value <0.1 in univariate analysis were entered in a Cox's stepwise regression model, adjusting covariates for time to CVC removal. Data are reported as of 31 January 2001. The SAS software package (SAS Institute, Cary, N.C., USA) was used for the analysis.

Results

During the study period, 129 CVCs were inserted in 112 children affected by leukemia and lymphoma (72 cases), solid tumors (34), and nonmalignant diseases (6): 65 (58%) were males and 47 (42%) were females. Their median age at CVC insertion was 4.9 years (range: 8 days–17 years). Among the malignant diseases, 83 (78.3%) were patients at their first diagnosis and 23 (21.7%) were at the diagnosis of relapse. Percutaneous and surgical placements were performed in 82 (63.6%) and 47 (36.4%) cases, respectively. Eleven patients (9.8%) had two and three patients (2.7%) had three CVCs inserted. Table 1 shows the main characteristics of the CVCs. The total number of CVC days was 19,328; the median period of observation per CVC was 122 days (range: 1–385). No complications were observed in 70 of 130 CVCs (53.8%).

At the end of the study period, 38 of 129 CVCs (29.5%) had been removed: 20 due to CVC-related complications, 10 due to the patient's death, and 8 on completion of therapy. The complications observed during the study were as follows.

Early complications

Of 82 CVCs inserted using the percutaneous technique, 2 (2.4%) were complicated by pneumothorax vs one of the 47 CVCs inserted using the cutdown technique. All three patients reported no symptoms, and the diagnosis was made on chest X-ray performed as part of the routine check on the CVC tip. All three patients were treated conservatively: two had a chest tube inserted and one had spontaneous resorption of a thin air layer. In another two cases, percutaneous CVC placement was complicated by arterial puncture.

Table 1 Main characteristics of the CVCs included in the study. *R* right, *L* left, *EJV* external jugular vein, *IJV* internal jugular vein, *SV* subclavian vein, *FV* femoral vein, *Saph V* saphenous vein

Number of lumens	Single lumen		68 (52.7%)	
	Two lumens		61 (47.3%)	
Insertion technique	Percutaneous		82 (63.6%)	
	Surgical		47 (36.4%)	
Diameter[a] (French)	Single lumen			
	4.2 Fr		29	
	6.6 Fr		30	
	9.6 Fr		6	
	Two lumens			
	7 Fr		49	
	9 Fr		13	
Cannulated vessel[b]	R-EJV	17	L-EJV	5
	R-IJV	64	L-IJV	7
	R-SV	29	L-SV	2
	R-FV	1	L-FV	0
	R-Saph V	2	L-Saph V	1

[a] Data available for 127 CVCs
[b] Data available for 128 CVCs

Table 2 Type and number of CVC-related complications observed during the study

Types of complication	Episodes (*n*)	Episodes/1000 CVC days
Infections		
Localized	31	1.6
Systemic	2	0.1
Subtotal	33	1.7
Malfunction	51	2.6
Partial/complete	38/13	–
Mechanical	36	1.9
Dislocation	30	–
Partial/complete	(12/18)	–
Rupture	4	–
Kinking	2	–
Subtotal	87	4.5
Total	120	6.2

Mechanical and infectious complications

Table 2 shows the type and incidence of all complications: there were 120 in all, as high as 6.2/1000 CVC days. The mechanical and infectious complications accounted for 87 (72.5%) and 33 (27.5%) of episodes, respectively, the incidence being 4.5/1000 and 1.7/1000 CVC days. No cases of CVC-related thrombosis were reported.

Table 3 Univariate and multivariate analysis of prognostic factors for premature CVC removal

Factors	Patient (%)	CVCs removed prematurely (*n*)	Univariate analysis *p*	Multivariate analysis *p*
Sex (male vs female)	79 (61.2) 50 (38.8)	16 vs 4	0.06	–
Median age at CVC positioning (≥4.9 vs <4.9 years)	63 (48.8) 66 (51.2)	5 vs 15	0.02	0.014
Diagnosis (leukemia/lymphoma vs other)	81 (62.8) 48 (37.2)	11 vs 9	n.s.	–
Positioning technique (surgical vs percutaneous)	47 (36.4) 82 (63.6)	11 vs 9	0.06	–
Number of lumens (single vs two lumens)	68 (52.7) 61 (47.3)	12 vs 8	n.s.	–
Cannulated vessel (subclavian vein vs other)	31 (24.2) 97 (75.8)	5 vs 15	n.s.	–
Diameter(≥7 French vs <7 French)	68 (53.5) 59 (46.5)	8 vs 12	0.2	–

Infectious complications

Two episodes of definite CVC-related bacteremia were recorded during the study both due to *Staphylococcus epidermidis*. Overall, the incidence of CVC-related bacteremia was 0.1 per 1000 CVC days.

There were 31 episodes of CVC-localized infections with an incidence of 1.6 episodes/1000 days of CVC use. Two were CVC tunnel infections, due to *S. epidermidis,* and 29 were CVC exit site infections: 23 of these were classified as presumed and 6 as definite infection, respectively. The germs isolated through skin swabs from the latter group were *S. epidermidis* (4), *S. aureus* (1), and *Klebsiella oxytoca* (1). Tunnel infections were successfully treated with i.v. teicoplanin for 7 days. All episodes of CVC exit site skin infection were successfully treated with topical application of rifampicin (24), teicoplanin (4), and gentamycin (1). Topical antibiotic treatment was administered for a median of 5 days (range: 2–15). None of these episodes required the removal of the CVC.

Mechanical complications

The most frequent mechanical complications were malfunction and dislocation. Fifty-one episodes of malfunction were recorded in 29 of 129 CVCs (22.5%), the incidence being 2.6 per 1000 CVC days. Malfunction was partial in 38 episodes and complete in 13. Of 51 episodes of malfunction (74.5%), 38 occurred over a 7-month period (April to October 2000) when a heparin flushing solution of 50 IU/ml was used instead of 200 IU/ml. CVC lumen patency was restored in all cases, using urokinase (38 episodes), alcohol (7 episodes), and hydrochloric acid (1 episode).

Other mechanical complications accounted for 36 episodes, their incidence being 1.9 per 1000 CVC days. These were dislocation (30) (complete 18, partial 12), ruptures (4), and kinking (2). The median time to occurrence of dislocation after CVC positioning was 52.5 days (range: 1–335). CVC removal was necessary in 20 episodes (dislocation 18, rupture 2). A conservative approach (securing the suture of the CVC to the skin at the exit site or repairing the externally damaged CVC tract) enabled CVC removal to be avoided in the remaining episodes.

Factors predicting premature CVC removal

In univariate analysis only median age <4.9 years at CVC insertion (p=0.02) proved significantly associated with premature CVC removal, while the results for the insertion technique and sex were close to significance (p=0.06). In multivariate analysis, only median age at CVC insertion <4.9 years remained a significant predictor of premature CVC removal [p=0.01, relative risk (RR) 3.6, confidence interval (CI) 1.3–9.9]. Table 3 summarizes the results.

Discussion

The need for a reliable vascular access is widely accepted in the management of patients affected by oncological and hematological diseases, especially in the pediatric field. The drawback of the widespread use of CVCs is the occurrence of complications such as infections, thrombosis, and CVC mechanical accidents that determine a longer hospital stay or may even become life threatening [16]. The main aims of this prospective study were to define the incidence and type of CVC-related complications at our center, to assess the efficacy of protocols used to treat these complications, and to identify the risk factors associated with premature CVC removal.

Some of our results deserve to be highlighted. First of all, mechanical complications were the most frequent, and dislocation was the main cause of premature CVC

removal. Other authors have recently reported similar data. Henrickson et al. found that the rate of CVC occlusion was greater than that of CVC infection in a group of pediatric patients randomized to CVC flushing with heparin solution, i.e., 3.99 vs 2.39/1000 CVC days, respectively [9]. In a prospective study on CVC complications, Fratino et al. observed that the rates of mechanical and infectious complications were 2.2 and 0.7/1000 CVC days, respectively, 9 of 12 CVC removals being due to dislocation [17].

Occlusion now rarely prompts CVC removal because potent fibrinolytic drugs [urokinase, recombinant human tissue plasminogen activator (rh-tPA)], or ethanol and hydrochloric acid are available for lysing clots or dissolving precipitates composed of lipids, salts, and incompatible drugs [13, 14, 18]. In all but one of our cases, a bolus of urokinase or other remedies were effective in clearing occluded CVC without having to resort to treatments that are more expensive either because of their higher purchase price (rh-tPA) or because they extend the hospital stay (continuous infusion of low-dose urokinase). In contrast to adult patients with indwelling CVC, no cases of CVC-related thrombosis were observed during the study, although no systemic anticoagulant prophylaxis was used [19]. There is no clear correlation in the literature between the concentration of heparin in the flushing solution and the incidence of CVC malfunction or CVC thrombosis [14, 16, 17, 19]. The greater frequency of CVC occlusions found with the less-concentrated heparin solution used during our study indicates that this issue deserves further investigation.

Accidental snatching plays a key part in causing CVC dislocation in two different ways, i.e., incomplete adhesion of the CVC Dacron cuff to the subcutaneous tunnel tissue in the early weeks after CVC positioning and the problems involved in restricting the physical activity of young children. Most CVC dislocations observed in this study happened during the first 2 months after CVC positioning, and younger age was the only significant factor in multivariate analysis associated with early CVC removal. These findings suggest that more effectively securing the CVC to the subcutaneous tissue at placement may significantly reduce the premature loss of CVC, especially in young children.

Many authors emphasize the importance of CVC-related infection, which accounts for 11–37% of hospital cases of bacteremia due to central lines [20]. It has been estimated that 14–51% of CVCs implanted in children with malignancies will be complicated by bacteremia, 35% by exit site infection and 2% by tunnel infection. The reported median incidence of CVC-related bacteremia is 2.5 episodes (range: 0.7–4.9) per 1000 CVC days and the attributable mortality is around 10%, mainly due to endocarditis, septic shock, pneumonitis, and septic thrombophlebitis [2, 21]. In our experience, the CVC infectious complications were only about one-fourth of all complications during the study period. The incidence of CVC-related bacteremia, 0.1/1000 CVC days, was far lower than the one reported in a recent pediatric randomized study, either in the arm in which the CVC was flushed with heparin alone (2.39/1000 CVC days) or in the arms that used heparin-vancomycin and heparin-ciprofloxacin-vancomycin flushing (0.5 and 0.64/1000 CVC days, respectively). Moreover, the rate of CVC exit site and tunnel infections was not influenced by the type of flushing solution, being 1.2 (vancomycin-heparin), 1.4 (heparin), and 1.5 (vancomycin-heparin-ciprofloxacin) per 1000 CVC days, respectively, similar to the one recorded in our study, which was 1.6/1000 CVC days [9]. These data suggest that CVC infection morbidity and mortality can be effectively prevented without adding to the cost of antibiotics. This issue is still a matter of debate, but other authors have confirmed the reliability of heparin without antibiotics as a flushing solution, providing an appropriate sterile CVC handling technique is used and staff are properly trained [22, 23].

Prompt empirical systemic antibiotic therapy enabled us to successfully treat both episodes of CVC-related bacteremia, showing that immediate CVC removal is not essential to prevent complications such as deep-seated infection and septic thrombophlebitis and to cure the patient. The decision to remove an infected CVC can consequently be postponed 48–72 h until a clinical and microbiological response to the antibiotic treatment has been observed [10, 24]. This strategy makes it possible to manage CVC-related infections more pragmatically, especially in pediatric oncology-hematology patients where thrombocytopenia and critical clinical conditions are serious obstacles to invasive procedures. Moreover, in stable patients responding to therapy, using an antibiotic lock technique may further reduce the hospital stay and cut costs [25].

In conclusion, this study shows that mechanical complications occur more frequently than infection in the life of a CVC, dislocation being the main cause of premature CVC loss. Younger age is the only prognostic factor negatively affecting CVC life span. These results emphasize the need to ensure excellent CVC fixation, especially in younger children, to minimize the effects of accidental traction during the first months after positioning. CVC infection remains an important cause of morbidity, but training staff to handle the CVC with proper aseptic techniques is still the most effective prevention measure. The role of antibiotics in the CVC flushing solution and the antibiotic lock technique is interesting, but requires further investigation.

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