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Original Article

Subcutaneously implanted central venous access device infection in pediatric patients with cancer

Miao-Chiu Hung, Chun-Jen Chen, Keh-Gong Wu, Giun-Yi Hung, Yu-Jan Lin, Ren-Bin Tang

Department of Pediatrics, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan

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Background and purpose: Subcutaneously implanted central venous access devices (SICVADs) are a common route of intravascular access for pediatric patients with cancer. This study was performed to evaluate the risk for SICVAD-related infection in a large consecutive series of unselected children with cancer in a single medical center.

Methods: The medical charts of 209 pediatric patients with cancer who received a SICVAD from January 1, 2001 to December 31, 2005 were retrospectively reviewed, and the patients were followed-up until June 30, 2006. The demographics, clinicopathologic features, and infectious complications were collected for analysis.

Results: There were 137,924 SICVAD days (median, 660 days; range, 16-1962 days). The rate of SICVAD-related infections was 0.15 episodes/1000 SICVAD days. There were 21 episodes of SICVAD-related infection among 17 patients, 18 were bloodstream infection among 14 patients and the other 3 were local infection among 3 patients. Sixteen SICVADs were removed, 13 were associated with bloodstream infection and 3 with local infection. Young age (<2 years) was associated with a high risk for SICVAD-related infection. Staphylococcal spp. and fungi were the most common pathogens associated with SICVADs.

Conclusions: The rate of SICVAD-related infection in children with cancer was low. Children younger than 2 years had a higher risk for SICVAD-related infection than older children. Fungi play an important role in SICVAD-related infection.

Key words: Catheters, indwelling; Child; Neoplasms; Wound infection

Introduction

A long-term central venous access device (CVAD) is convenient for children with cancer who need frequent blood sampling, chemotherapy, hydration, or parenteral nutrition [1]. Polymeric silicone catheters were introduced for total parenteral nutrition in 1973, followed by long-term venous access, which became available in 1977, and subcutaneously implanted CVADs (SICVADs) were developed in 1982 [2]. The advantages of SICVADs include fewer infectious and thrombotic complications, improved body image, and decreased anxiety associated with treatment. In addition, SICVADs also need less maintenance than other devices, only requiring monthly flushing with heparin [3,4].

Complications such as infection, thrombosis and catheter break associated with SICVADs have previously been reported in different disease groups [5-9]. Catheter-related bloodstream infection has been reported at a rate of 0.1 to 2.9 episodes/1000 catheter days [5]. The objective of this study was to evaluate the risk of infection associated with SICVADs in a large consecutive series of unselected children with cancer in a single medical center.

Corresponding author: Dr. Keh-Gong Wu, Department of Pediatrics, Taipei Veterans General Hospital, No. 201, Section 2, Shih Pai Road, Taipei 112, Taiwan.
E-mail: kgwu@vghtpe.gov.tw

Methods

Patients

212 pediatric patients with cancer were implanted with an SICVAD at Taipei Veterans General Hospital, Taipei, Taiwan, from January 1, 2001 to December

31, 2005. Three patients were excluded from the study due to loss to follow-up. The medical charts of 209 consecutive pediatric patients with cancer who received SICVADs during this period were retrospectively reviewed, and the patients were followed-up until June 30, 2006. There were 228 SICVADs among the 209 patients. The BardPort© (Bard Access Systems, Salt Lake City, UT, USA) was the most commonly implanted device (n = 195; 85.5%).

All the SICVADs were implanted under general anesthesia by experienced pediatric surgeons. There were no serious perioperative complications. The SICVADs were flushed with heparinized normal saline at least once a month. All parenteral medications, nutrition fluids, and blood product transfusions were administered through the device. Most of the blood sampling was also obtained via the device.

Definition of infection

SICVAD-related bloodstream infection was defined as follows: paired blood cultures from the device and percutaneous vessels showing different pathogens from any other infectious focus (pneumonia, urinary tract infection); clinical presentation of fever, chills, or hypotension; and pathogens isolated from the catheter tip upon removal [10]. Quantitative blood culture was not done at Taipei Veterans General Hospital. Nevertheless, if the SICVAD was removed for suspected infection, the catheter tip was cultured by the roll-plate semiquantitative method. The criteria of Randolph et al [11] and O'Grady et al [12] were used to categorize the diagnosis as definite, probable, or possible (Table 1).

Pocket infection was defined as infected fluid in the subcutaneous pocket and was often associated with tenderness, erythema, and/or induration over the pocket [10]. In the absence of a positive blood culture, this was defined as local infection.

Statistical analysis

The Z-test was used to compare the proposed risk factors of age, sex, and underlying disease between the infection group (n = 17) and the non-infection group (n = 192).

Results

The median age of the patients at implantation of the SICVAD was 8.0 years (range, 16 days to 16.8 years). 133 patients (64%) were boys and 76 (36%) were girls. The most common types of cancer were tumor of the central nervous system (n = 98; 47.0%) and osteosarcoma (n = 34; 16.0%), followed by leukemia (n = 33; 16.0%), non-Hodgkin's lymphoma (n = 6; 2.9%), retinoblastoma (n = 6; 2.9%), histiocytosis (n = 6; 2.9%), Hodgkin's lymphoma (n = 5; 2.4%), rhabdomyosarcoma (n = 5; 2.4%), neuroblastoma (n = 4; 1.9%), germ cell tumor (n = 3; 1.4%), synovial sarcoma (n = 2; 1.0%), Ewing sarcoma (n = 1; 0.5%), hepatoblastoma (n = 1; 0.5%), primitive neuroectodermal tumor (n = 1; 0.5%), clear cell sarcoma of bone (n = 1; 0.5%), and sarcoma (n = 3; 1.4%). The median and total observation times for the SICVAD were 597 days (range, 16-1962 days) and 137,924 days, respectively.

Catheter-related bloodstream infection and local infection

There were 21 episodes of SICVAD-related infection among 17 patients. There were 0.15 episodes of SICVAD-related bloodstream infection/1000 SICVAD

Table 1. Clinical definition for catheter-related bloodstream infection. Adapted from Muscedere et al [7] and van den Berg et al [8].

Definite catheter-related bloodstream infection

One of the following should be present in addition to at least 1 peripheral positive blood culture:

1. Pus from the catheter exit site, growing the same microorganism as peripheral blood

Probable catheter-related bloodstream infection. Either 1 or 2 of the following criteria should be met:

1. Clinical catheter-related sepsis: positive (semi-) quantitative catheter tip to segment culture in a patient with clinical sepsis and no other apparent source than the catheter that resolves within 48 h of catheter removal in the absence of new antibiotic therapy
2. Bacteremia/fungemia: at least 2 positive blood cultures, including 1 peripheral with a common skin commensal, in a patient with an intravascular catheter and clinical manifestation of infection (fever, chills, and/or hypotension), in the absence of catheter segment culture and no apparent source for the bloodstream infection except the catheter

Possible catheter-related bloodstream infection. Either 1 or 2 of the following criteria should be met:

1. Clinical catheter-related sepsis: positive (semi-) quantitative catheter tip or segment culture in a patient with clinical sepsis and no other apparent source than the catheter that resolves after catheter removal and initiation of antibiotic therapy
2. Bacteremia/fungemia: at least 1 positive blood culture, either through the catheter or peripheral, with a common skin commensal in a patient with an intravascular catheter and clinical manifestations of infection, in the absence of catheter segment culture and no apparent source for the bloodstream infection except the catheter

days. The average time from implantation to development of infection was 174.8 days (range, 7-625 days). Three patients had local infections (1 episode each), which occurred an average of 23 days after implantation; the 3 devices were removed. Eighteen episodes were SICVAD-related bloodstream infection and 13 of the SICVADs were removed. Table 2 summarizes the characteristics of patients with SICVAD-related infection and the pathogens isolated.

The 3 local infections were caused by *Staphylococcus aureus*. The 18 episodes of SICVAD-related bloodstream infection were caused by *Candida* (n = 3; 16.6%), yeast-like pathogens (n = 3; 16.6%), *S. aureus* (n = 3; 11%), *Burkholderia cepacia* (n = 2; 11.1%), coagulase-negative staphylococci (n = 3; 5.5%), *Enterobacter cloacae* (n = 2; 11.1%), and *Serratia rubidata* (n = 2; 11.1%).

Young children were at higher risk for SICVAD-related infection than older children. Ten of 17 patients with SICVAD infection were younger than 2 years compared with only 25 of 192 patients younger than 2 years in the non-infectious group ($p < 0.01$). There were no differences in the type of malignancy or the sex of the patients between the groups.

Discussion

This study is one of the largest to evaluate SICVAD-related infection among pediatric patients with cancer. Hengartner et al's study showed that the infection rate of central venous ports among different diseases ranged from 0.10 to 1.43/1000 SICVAD days [5]. The overall SICVAD-related infection rate in this study was 0.15 episodes/1000 SICVAD days, which is lower than that of most reported studies [5-7,13].

According to Hengartner et al [5] and Rogier et al [14], young age, intensive chemotherapy complicated with severe neutropenia, and frequent blood sampling or infusion medication administered via the SICVAD were the major risk factors for SICVAD-related infection. This study also found that young age was associated with high risk for SICVAD-related infection. This could be attributed to young children's immature immune systems, difference in skin temperature and type of skin pathogens, and difference in immune responses of young children to foreign bodies [14].

Three SICVADs were removed within 36 days of implantation (average, 23 days) because of local infections, which were due to postoperative infection and/or impaired wound healing during chemotherapy. However, it is difficult to evaluate SICVAD-related bloodstream infection, as the skin around the insertion site is easily colonized with several microorganisms. Tweddle et al found that there was wide variation in defining the colonization of central venous catheters by questionnaires [15]. It is well accepted that catheter-related bloodstream infection is defined as the same microorganism isolated from blood and the catheter [5,10]. Painful peripheral blood sampling is undesirable for pediatric patients, so there was some difficulty in obtaining peripheral blood for culture before the initiation of antimicrobial agents. Gaur et al developed a new diagnostic strategy of detecting the difference in time (>180 min) to positivity of blood cultures taken concurrently from 2 lumens of a multilumen central venous catheter [16]. As a result, the positive predictive value of catheter-related bloodstream infection ranged from 81% to 93% and the negative predictive value ranged from 67% to 86%. However, this approach is not applicable to SICVAD infection.

Previous studies have found that the most common microorganisms of SICVAD-related infection were CoNS or *S. aureus* [3,5,17-20]. However, the most common microorganism of bloodstream infection in this study was fungus (6 of 18 episodes; 33%). Six episodes of SICVAD-related bloodstream infection caused by fungus occurred in 5 patients, all of whom had a history of prior broad-spectrum antibiotic treatment, but no history of total parenteral nutrition infusion, intensive care unit stay, or previous colonization of fungus.

The indications for removal of SICVADs have been discussed in previous reports [1,10,20,21]. Schwarz et al suggested the following indications for SICVAD removal: port pocket infection, hemodynamic instability of sepsis, septic emboli, device no longer necessary, primary attending physician's request, and dysfunctional device [1]. Other indications include recurrent infection with the same microorganism and fungal infection of the SICVAD without fungemia or sepsis. Rubin et al suggested that most SICVAD-associated bloodstream infection in pediatric patients with cancer can be cured without device removal [20]. However, according to the guideline from the Infectious Diseases Society of America, removal of the device should be considered for patients with a central line infected by *Candida* spp. [10]. Shah et al also suggested removal of a CVAD if there is tunnel infection, the patient is critically ill, the bacteria are not

Table 2. Clinical and laboratory characteristics of 21 episodes of subcutaneously implanted central venous access device (SICVAD)–related infection (n = 17).

Patient no.	Age at implantation	Cancer type	Infection type	Clinical definition	Time between implantation and removal (days)	Culture site and microorganisms isolated	Removal of SICVAD
1a	12 years 1 month	Acute myeloid leukemia (M4)	Systemic	Possible	51	Blood: *Candida albicans*	Yes
1b	12 years 2 months	Acute myeloid leukemia (M4)	Systemic	Probable	98	Blood: *Candida tropicalis*	Yes
2	5 years 6 months	Non-Hodgkin's lymphoma	Systemic	Probable	233	Tip: *C. albicans*	Yes
3	8 years 6 months	Acute lymphoblastic leukemia (T-cell)	Systemic	1: possible 2: probable	166	Blood: *Enterobacter cloacae*	Yes
4	1 year 4 months	Primitive neuroectodermal tumor, cerebellum	Systemic	Possible	64	Blood: *Burkholderia cepacia*	Yes
5	16 days	Atypical teratoid/ rhabdoid tumor	Systemic	Possible	17	Tip/pus/blood: MRSA	Yes
6	1 year 8 months	Primitive neuroectodermal tumor, right thalamus	Systemic	Possible	281	Blood: yeast-like	Yes
7	9 years 6 months	Germ cell tumor, suprasellar area	Systemic	Definite	196	Tip/blood: yeast-like	Yes
8	1 year 6 months	Anaplastic ependymoma	Systemic	Probable	217	Blood: yeast-like	Yes
9	54 days	Atypical teratoid/ rhabdoid tumor	Systemic	Definite	9	Blood/pus/tip: MSSA	Yes
10	10 months	Pilocytic astrocytoma	Systemic	1: possible 2: probable	318	Blood: *Serratia rubidata*	Yes
11	11 years 2 months	Mixed germ cell tumor	Systemic	Possible	529	Blood: *B. cepacia*	Yes
12	64 days	Rhabdomyosarcoma	Systemic	Possible	625	Tip: coagulase-negative staphylococci	Yes
13	2 years 6 months	Mixed germ cell tumor over presacral area	Systemic	Possible	-	Pus/blood: MRSA	No
14	1 year 6 months	Acute lymphoblastic leukemia	Systemic	1: possible 2: possible	-	Blood: *Staphylococcus epidermidis*	No
15	21 days	Poorly differentiated malignant tumor with focal neuroepithelial differentiation	Focal	-	9	Pus: MRSA	Yes
16	2 years 1 month	Pilocytic astrocytoma	Focal	-	23	Pus: MSSA	Yes
17	10 years 10 months	Low-grade astrocytoma	Focal	-	14	Pus: MSSA	Yes

Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *S. aureus*.

cleared within 48 to 72 h, there are persistent symptoms beyond 48 to 72 h, the patient has endocarditis, metastatic infection, or septic thrombophlebitis, or bloodstream infection is caused by *S. aureus*, *Candida* spp., *or* mycobacteria [21].

In this series, almost all the patients who had fungemia, repeat infection, or relatively poor response to antibiotic treatment underwent removal of the SICVAD. There were 2 exceptions: 1 patient with intracranial germ cell tumor who had local infection and secondary bloodstream infection caused by *S. aureus* was successfully treated by systemic antibiotics without the need for removal of the SICVAD. The other patient had acute lymphoblastic leukemia and had SICVAD-related bloodstream infection caused by *Staphylococcus epidermidis* twice, which was also successfully treated by parenteral antibiotics. Both patients' SICVADs were removed 2.4 and 6.5 months later due to obstruction of the line. Infection of an SICVAD is related to subsequent thrombosis formation and obstruction, which is compatible with Rooden et al's study [22]. The relationship between thrombosis and infection is thought to be bidirectional. Microorganisms tend to adhere to thrombi, although catheter-related infection may initiate an inflammatory response inducing excessive thrombus formation [22].

Strategies to prevent CVAD-related infections include cutaneous antisepsis, maximizing the sterile barrier, and use of antimicrobial-coated catheters or antimicrobial catheter lock solutions [23]. Rubie et al successfully used a vancomycin flushing lock in patients with cancer and decreased the rate of *S. epidermidis* bloodstream infection from 0.80 to 0.17 cases/1000 device days during a 3-year study [24]. A meta-analysis of 7 randomized controlled trials showed that the use of a vancomycin lock solution for patients requiring long-term central venous catheters reduced the rate of catheter-related bloodstream infection [23]. However, their use should be reserved for those who require indefinite vascular access [25].

The limitations of this study include its retrospective design. As all the data were collected from a single institute, further large series or a multicenter study would provide more information.

In conclusion, SICVADs are convenient and safe devices for pediatric patients with cancer. Young age (<2 years) is associated with a high risk for SICVAD-related infection. With the use of broad-spectrum antibiotics, fungi played an important role in SICVAD-related bloodstream infection in this series. The exact mechanisms and preventive measures for SICVAD bloodstream infection require further study to reduce infection rates.

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