Infectious complications and conservative treatment of totally implantable venous access devices in children with cancer

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Besides their complications, totally implantable venous access devices (TIVADs) increase the quality of life in children with cancer. The aim of this study was analysis of infectious complications and results of conservative management in TIVADs. Three hundred and one catheters were implanted in 283 patients between February 1991 and January 2005. Infectious complications were analyzed retrospectively. Cumulative duration of implantation was 153,757 days. In 140 devices (46.5%), no complication was detected. Total rate of infection was 1.96/1000 catheter days. Types of infections were as follows: catheter-related bloodstream infections: 190; catheter-related systemic infections: 74; pocket infections: 19, exit site infections: 14; and tunnel infections: 5. *Staphylococcus epidermidis* and non-albicans candida were the most common isolations. During follow-up, a total of 119 catheters had been removed. Most of them were due to infection (n=42). In conclusion, TIVADs are important in children with cancer who need prolonged intravenous access, so they should be used carefully and managed conservatively in case of complications.

Key words: totally implantable venous access devices, infection, pediatric cancer.

In oncology practice, use of totally implantable venous access devices (TIVADs) for prolonged venous access has increased since the 1980s. Despite their serious complications, they have substantially increased compliance to treatment and quality of life of children with cancer. They also provide significant convenience to the medical staff regarding vascular interventions.

There are two types of long-term vascular devices. These are tunneled catheters (e.g. Hickman, Broviac type catheters) and TIVADs. TIVADs are long-term catheters that are composed of a reservoir and a catheter. The reservoir is surgically placed under the skin and a catheter is attached to the reservoir. The catheter is tunneled beneath the skin to be implanted in the subclavian or internal jugular vein. These devices are accessed with a needle through a silicon membrane on the reservoir. Reservoirs are usually composed of polyurethane, steel or titanium. Both TIVADs and tunneled catheters have different properties and care recommendations. TIVADs are generally preferred because of their relatively lower infection rate, their easy use and infrequent requirement of catheter care by the medical staff.

Long-term catheters have different complications, including infections and mechanical complications such as occlusion and thrombosis. Infections are very common complications. The most common isolates associated with catheter infections are gram-positive microorganisms. Acceptable success rates for short-term eradication of catheter-related bloodstream infections (CRBSI) without catheter removal had been reported with conservative management, especially in infections with coagulase-negative staphylococci[1,2]. Catheter salvage with various infections such as Candida and gram-negative infections are usually discouraged but exceptions do exist in the literature[3,4].

The goals of this study were evaluation of the frequency of infectious complications and

results of conservative management of TIVADs in children with cancer. Some of the probable factors for infection are also overviewed.

Material and Methods

Medical records of children who had been admitted to Hacettepe University, Department of Pediatric Oncology, between February 1991 and January 2005 were evaluated retrospectively for TIVAD-related complications. The study was conducted retrospectively between 2004 and 2005.

Twenty-nine of the TIVADs were Port-a-Cath® and 255 were Braun®. In the retrospective medical records, the type of port catheters had not been defined in 17 TIVADs. No analysis was performed according to types of TIVADs.

Infections associated with catheters were defined in several reviews based on the Hospital Infection Control Practices Advisory Committee (HICPAC) recommendations[5-7]. In this study, infections were classified as Ingram et al.[8] had previously mentioned. In case of fever with no other focal infection, two isolations of coagulase-negative staphylococci or any other positive blood culture except coagulase-negative staphylococci were defined as 'proven' CRBSI. In the presence of fever without an origin, with clinical signs of septicemia, simultaneous positive blood cultures both from catheters and peripheral veins were defined as catheter-related systemic infection (CRSI) or catheter-related septicemia. Erythema, induration and/or tenderness within 2 cm in diameter around the port catheter needle were accepted as exit site infection (ESI). Infection involving skin, subcutaneous soft tissue and abscess formation around the reservoir of the port catheter was described as pocket infection (PI). Subcutaneous erythema, tenderness and induration more than 2 cm from the reservoir and catheter exit site and extending along the catheter were defined as tunnel infection.

The data variables that were recorded in this retrospective study are given in Table I.

The frequency, mean and median values and cross-tables were used for descriptive statistics. Complication rates were calculated according to 1,000 catheter days (cd) by using frequency of complications and cumulative cd. The number of complications from all catheters was divided by cumulative experience (as days), and

Table I. Data Retrieved Retrospectively in this Study

Age
Gender
Tumor diagnosis
Dates of tumor diagnosis,insertion and removal of catheters and last visit of patients with catheters
Type of insertion technique (surgery or interventional radiology)
Type of port catheter
Total number of port catheters per patient
Cumulative experience of catheter days
Types and dates of infectious complications
Catheter related blood stream infection
Catheter related systemic infection-sepsis
Exit site infection
Tunnel infection
Pocket infection
Outcome and functional status of port catheters after complications
Isolated microorganisms
Status of the catheter after isolation of microorganisms
Neutropenic status during infections
Total number of positive cultures
Isolated microorganisms from the tip cultures of the removed catheters
Distribution of port insertions according to time frames (1991-1995; 1996-2000; 2001-2004)
Reason of catheter removal

multiplied by 1,000 cd. Mann-Whitney U test was used for comparison of complication rates between different insertion techniques. One-way ANOVA test was preferred for comparison of mean complication rates according to age groups.

Results

Over 14 years, 301 port catheters were inserted in 283 patients. Some important clinical characteristics of the patients are given in Table II. During 153,757 cd, 302 infection episodes involving 161 ports were detected. Neutropenia accompanied 121 infection episodes (40.1%). Ninety-seven of 302 infections were detected in the first month of catheter insertion (30.5%). The total rate of infectious complications was 1.96/1000 cd. Some important characteristics of the catheter infections and isolated microorganisms are displayed in Table III and Table IV, respectively. Age, catheter insertion period and insertion technique had no effect on infection rates.

Forty-two of 301 catheters were removed due to infection. In five cases, both infection and catheter occlusion were the main reasons for removal. The leading type of infection in removed catheters was CRBSI.

Table II. Some Important Characteristics of 283 Patients with Port Catheters

	n	%
Male sex	166	58.7
Age groups		
<2 years	117	41.3
3-6 years	73	25.8
7-10 years	40	14.1
>10 years	53	18.8
Primary diagnosis		
Non-Hodgkin's lymphoma	103	36.4
Neuroblastoma	56	19.8
Rhabdomyosarcoma	31	11.0
Brain tumors	18	6.4
Retinoblastoma	13	4.6
Wilms' tumor	10	3.5
Other childhood malignant tumors	70	23,3
Number of TIVADs per patient		
One	266	94
Two	16	5.7
Three	1	0.3
Total (# of patients)	283	100
Catheter insertion technique		
Interventional Radiology	16	5.3
Surgery	285	94.7
Time frames of TIVAD insertion		
2001-2004	190	63.1
1996-2000	92	30.6
1991-1995	19	6.3
Total (# of catheters)	301	100

Table III. Infection Rates According to Types of Infection and Clinical Conditions

	n	Rate*
Total number of infectious episodes	302	1.96
Infection types		
Catheter-related blood stream infection (CRBSI)	190	1.24
Catheter-related systemic infection (CRSI)	74	0.48
Pocket infection	19	0.12
Exit site infection (ESI)	14	0.09
Tunnel infection	5	0.03
Age group		
<2 years	117	1.73
3-6 years	73	2.45
7-10 years	40	2.37
>10 years	53	1.39

* Number of infections / 1,000 catheter days

The results of conservative management approach to infected catheters are given in Table V. One hundred and fifty-four catheter-related infections were cured (51%) (Table V). Salvage rates were better in ESI (85.7%). In CRBSI, recurrent infections were detected both with the same and different types of microorganisms (16.8% vs 12.6%, respectively). Tip cultures had been studied in 37 removed catheters. Twenty-nine positive isolations were detected from catheter tips (29/37, 69%). The most common isolated microorganisms were *Staphylococcus epidermidis, S. aureus,* albicans, and non-albicans candida.

Ten patients died following catheter-related infections. Systemic sepsis in seven, CRBSI in two and pocket infection in one patient were recorded as initial manifestations of these subsequent events. There were nine isolations from tip cultures (*S. aureus* in 5, Candida in 4 patients). Six patients also had primary disease relapse at the time of death.

Discussion

In this retrospective study, we found a high overall infection rate. In studies that examined both TIVADs and external central venous catheters, infection rates varied from 2.19 to 4.25/1000 cd[2,9-11]. Evidence had shown that infection rates were lower in case of port catheters [10,11], whereas in four studies, two with children, no difference was detected[12-15]. A comparison of device-associated infections in pediatric patients is outlined in Table VI. It should be considered that both number of TIVADs and cumulative experience were relatively higher in the current study[9-11,16,18-20,21-25]. Adler et al.[1], with 240 TIVADs, reported the infection rate as 1.45/1000 cd, with a median 277 cd. In our experience, with approximately two-fold cumulative cd, a higher infection rate had emerged. Although it was difficult to conclude that longer use was associated with a higher infection rates, this issue should be investigated with further studies.

Higher catheter-associated infection rates were detected in pediatric patients[2,9,26,27]. In our study, catheters had been used in a relatively young population compared with other studies [2,9,16]. The median age was four years, and 117 cases were younger than two years. Although statistically insignificant, the infection rate was relatively higher in this group. If high infection rates were associated with young age, distribution of the patients according to age groups might have contributed to this issue.

Gram-positive cocci were the most common isolated microorganisms in catheter-related infections. In pediatric series, isolated serotypes were *S. epidermidis*, methicillin-sensitive and methicillin-resistant *S. aureus* (MSSA, MRSA)[9,10,16,17,23,28]. In our experience, 65% of isolations were gram-positive and approximately 70% of gram-positive microorganisms were *S. epidermidis*. Microbiological documentation of a pediatric study showed mainly gram- negative

Table IV. Isolated Microorganisms

	n	%
Coagulase-negative staphylococci	138	
S. epidermidis	76	26.3
S. hominis	17	5.9
S. saprophyticus	16	5.6
Other staphylococci	29	10
Other gram-positive microorganisms	49	
Staphylococcus aureus	20	7
Enterococcus spp.	14	4.9
Streptococcus spp.	9	3.1
Micrococcus spp.	6	2.1
Gram-negative microorganisms	49	
Klebsiella spp.	9	3.1
Enterobacter spp.	8	2.8
Pseudomonas spp.	7	2.4
Serratia marcescens	7	2.4
Escherichia coli	4	1.4
Acinetobacter spp.	4	1.4
Stenotrophomonas maltophilia	4	1.4
Pantoea agglomerans	2	0.8
Other gram-negative microorganisms	4	
Fungi	52	
Non-albicans candida	32	11.1
C. albicans	20	7
Total	288	100
Tip cultures of removed catheters		
No isolation	8	21
S. epidermidis	7	18.9
Non-albicans candida	5	13.5
S. aureus	5	13.5
C. albicans	4	10.8
S. marcescens	2	5.4
Pseudomonas aeruginosa	1	2.7
E. coli	1	2.7
S. maltophilia	1	2.7
Micrococcus sedentarius	1	2.7
Staphylococcus capitis	1	2.7
Enterobacter cloacae	1	2.7

agents in external catheters and gram-positive microorganisms in TIVADs[2]. In the series of Hollyoak et al.[9] MSSA, *S. epidermidis,* and MRSA were the three most common agents in tip cultures. We detected 29 positive tip cultures. Besides gram-positive microorganisms, both non-albicans and *Candida albicans* were frequently detected. In our institution, in the

Table V. Treatment Results of Infected Catheters

	n	%
Treatment rates in total infection episodes	301	50.99
Catheter-related blood stream infections	190	57.89
Catheter-related systemic septicemia	74	33.78
Exit site infection	14	85.71
Pocket infection	19	26.32
Tunnel infection	5	40.00

n: number of infectious episodes

Table VI. Important Studies on Catheter-Related Infections in the Literature

	Number of port catheters	Cumulative catheter days	Infection rate*	Catheter removal rate**
Pegelow et al.[20]	15	4,094	0.49	13.3
Raj et al.[25]	18	19,230	0	0
McGovern et al.[19]	39	6,724	0.4	7.7
Krul et al. [21]	42	n.a.	n.a.	2.4
Babu et al.[24]	55	#750	n.a.	3.6
Severien et al.[10]	75	9,611	0.5	12
Wesenberg et al.[18]	77	64,025	0.11	3.9
McMahon et al.[23]	86	n.a.	n.a.	31.4
Sola et al.[16]	135	45,098	0.35	6.7
Hollyoak et al.[9]	239	#257	1.11	29.7
Adler et al. [11]	243	#277	1.45	23.5
Wiener et al. [22]	290	189,495	n.a.	1.72
Current Study	301	153,757 (#467)	1.96	13.95

*: number of infections in 1,000 catheter days; **: catheter removal rate due to complications
#: median experience was reported in some of the studies.
n.a: data not available

Department of Hematology, 134 BSIs, including 30.4% *Escherichia coli,* 32.1% MSSA, and 25% *C. albicans* were reported in adults[29]. In a multicenter study of adult intensive care units including our hospital, CRBSIs ranged from 5.3-41.5 per 1000 cd. Isolated microorganisms were Acinetobacter spp. in 23.2%, *S. aureus* in 23.2%, Enterobacteriaceae in 19.6%, coagulase-negative staphylococci in 12.2%, Pseudomonas spp. in 11%, and Candida in 3.4%. However, it should be considered that the patient population was not uniformly distributed according to primary disease and type of device used[30].

In uncomplicated catheter-associated infections, except sepsis, proven isolations of mycobacteria, yeasts or resistant gram-negative bacteria, treatment with antibiotics and preservation of the catheter in case of elimination of infection represent an accepted management according to several guidelines[5-7,31]. Catheter preservation following treatment of catheter-associated infections reached 60-80% in adults[27,32]. In this study, 51% of the catheters kept their function after treatment of infections with empirical antimicrobial therapy. Adler et al.[2] and Wang et al.[33] reported 63.7% and 57% catheter salvage rates, respectively, with empirical antibiotic treatment. Recurrent infections following systemic antibiotics are an expected issue because of colonization and biofilm formation inside the catheter. The recurrent infection rate was 51% in a similar study[2]. The recurrent infection rate was 41.1% with the same and 28.8% with other agents in this study.

Catheter removal because of infection was 14% in 301 TIVADs. A relatively low number

of catheters were removed despite the high infection rate. In another study from our institution involving adult patients, removal of TIVADs due to late complications was seen in 7.6%[34]. In two reports involving pediatric patients, more than 200 catheters were examined, and infection rates were 1.45 and 1.1/1000 cd, and removal due to infection was noted in 23.5% and 29.7%, respectively[2,9] (Table VI).

Mortality related with catheter-associated infections was 2.8% and 3.5% in two different studies[2,28]. Six cases were fatal in another pediatric series with 32 infectious complications [10]. In our experience, catheter complications led to death in 12 cases (3.3%). In 6 patients, recurrence of primary disease and neutropenia had also contributed to mortality.

In conclusion, a low number of catheters had to be removed due to high infection rates with empirical antimicrobial treatment in order to preserve 'valuable' devices in the practice of pediatric oncology, without an increase in mortality. Special considerations are important for the prevention of infections. The first and most important issue should be education of the 'changing' medical staff who deal with catheters. Caregivers should also be educated regarding the insertion of catheter needles with sterile technique during both inpatient and outpatient care.

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