ORIGINAL ARTICLE

Hemodialysis Catheter-Related Infections among Pediatric Patients in Mansoura University Children Hospital

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Key words:
Hemodialysis; CVC-RI; Incidence; Infection control

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ABSTRACT

Background: *Infection is the second leading cause of death in patients on hemodialysis (HD) after cardiovascular disease. Using a central venous catheter (CVC) is the most important risk factor for blood stream infection in HD patients, which can lead to life-threatening complications. Central venous catheter related infections (CVC-RI) may be local access site infection (LASI) or access related blood stream infection (ARBSI).* ***Objectives:*** *We performed a descriptive longitudinal (prospective) study to detect incidence of hemodialysis CVC-RI in Mansoura University Children Hospital (MUCH), determine risk factors and provide appropriate infection control interventions.* ***Methodology:*** *A total of 114 hemodialysis catheters were collected from 100 patients with CVC inserted more than 48 hours.* ***Results:*** *From the 114 collected, 27 (23.7%) CVC-RI were documented with incidence of 8.6 per 1000 CVC-days. Among these CVC-RI, 24 were LASI (21.1%, 7.7 per 1000 CVC-days) and 3 were ARBSI (2.6%, 0.9 per 1000 CVC-days). The commonest micro-organism detected causing CVC-RI was staphylococcus aureus.* ***Conclusions:*** *Femoral catheters, associated co-morbidities as D.M and immunosuppression and low compliance to preventive measures of infection during maintenance of the catheters were significant risk factors for CVC-RIs.*

INTRODUCTION

Hemodialysis (HD) is the preferred renal replacement therapy for patients requiring dialysis on a short-term basis, and for many patients who require maintenance dialysis. The central venous catheter (CVC), arteriovenous fistula (AVF), and arteriovenous graft (AVG) are the three main forms of vascular access utilized for HD [1]. HD catheters have become critical tools in the management of end-stage renal disease (ESRD) patients when HD is required but AVF and AVG are unavailable, maturing, or deteriorating [2]. Temporary vascular access by CVC is widely used in HD. However, CVC is associated with complications as infection, which can result in life-threatening complications [3]. Central venous catheter related infection (CVC-RI) may be local access site infection (LASI) or access related blood stream infection (ARBSI). LASI is suspected in patients who develop tenderness, erythema, purulent discharge, or local hotness at the catheter site. ARBSI is suspected in patients with CVCs who have the clinical or laboratory criteria of the systemic inflammatory reaction either rigors are present or absent[4]. Most of ARBSIs are caused by Gram-positive organisms, including coagulase-negative *Staphylococci*, *Staphylococcus aureus (S. aureus)*, and *Enterococcus*. A broad spectrum of Gram-negative organisms as *Klebsiella pneumonia*, *Acinetobacter baumanii*, *Escherichia coli* and *Proteus mirabilis* accounts for 20%–30% of patients [5]. Risk factors leading to hemodialysis CVC-RI are prolonged use of the catheter, a history of previous ARBSIs, recent surgery, diabetes mellitus, iron overload, immunosuppression, and hypoalbuminemia [6]. The current study's goal was to detect the incidence of CVC-RI in hemodialysis children, determine the risk factors for developing CVC-RI in the cohort of hemodialysis children and provide appropriate infection control interventions that are locally effective.

METHODOLOGY

Study population:

The current study was a descriptive longitudinal (prospective) study performed in Medical Microbiology and immunology Department, Faculty of Medicine, Mansoura University, through a period of 18 months from August 2019 till January 2021 on 100 hemodialysis pediatric patients with CVC inserted more than 48 hours in Mansoura University Children Hospital (MUCH). Patients who had sepsis due to causes other than catheter related blood stream infections were excluded.

Data collection:

The following informations were gathered from the patients: name, age, gender, residence, associated comorbidities (as diabetes, immunosuppression, hypertension and malignancy), presence of signs of

systemic infection (as fever, chills, hypotension), presence of signs of local infection (as purulent discharge, tenderness, erythema, local hotness at CVC site), previous antibiotic use, CVC insertion date and site of insertion of CVC.

Observation of hygiene measures:

The measures observed were hand hygiene, wearing mask, putting on sterile gloves, applying skin antiseptic and utilizing sterile drapes. These measures were observed during insertion and maintenance of the catheters.

Case definitions:

A patient was deemed to have CVC-RI if either LASI or ARBSI was developed. The diagnosis of LASI required a positive culture of the catheter segment by quantitative method (more than 10^3 CFU / ml) with infection signs at the catheter insertion site. ARBSI was diagnosed in accordance with the criteria of the Centers for Disease Control and Prevention (CDC) as one or more positive blood cultures and a positive catheter tip culture, whereby the same organism with the same species, had the same characters and antibiotic sensitivity is isolated and not related to another site of infection [7]. The incidence of hemodialysis CVC-RI was calculated as an incidence per 1000 catheter-days.

Microbiological methods:

Hemodialysis children were followed up after the insertion CVCs for any sign of infection; if there was any sign of infection, the samples (catheter tip, central and peripheral blood, and swab from pus if present) were collected for microbiological examination. We cultured catheter tips by the quantitative method described by Brun-Buisson et al [8]. Detection of $\geq 10^3$ colony forming units (CFU) / ml of broth cultures in absence of accompanying signs of infection at the catheter insertion site was considered catheter colonization while detection of $\geq 10^3$ CFU / ml of broth culture with infection signs at the catheter insertion site was indicative of LASI. On the contrary, contamination of a CVC was assumed when fewer CFUs than 10^3. For collecting central blood: 2-3 ml blood was collected aseptically from the port immediately after removing the catheter. Peripheral blood was obtained by the following method: the vein was palpated before skin disinfection. Once the vein has been chosen, skin was disinfected with 70% alcohol and 2% tincture iodine in the puncture site and 2-3 ml of blood was collected aseptically. Blood was inoculated directly into a blood culture bottle that was labeled and then transmitted to MDICU for aerobic incubation at 37º C for further processing [9]. The purulent discharge was collected by a sterile swab by rotating maneuver with pressure for extracting fluid. In the event of an anticipated delay of processing, Stuart transport medium was used and sent for further processing [9]. Isolation and Identification of organisms was done by colony characteristics, Gram-stained films, and biochemical reactions. Antibacterial susceptibility testing by disc diffusion method was done for the isolated organisms. Antibiotic discs were selected in accordance with the recommendations of Clinical and Laboratory Standards Institute (CLSI) [10].

Ethical approval:

The protocol of this study was accepted by Institutional Review Board (IRB), Faculty of Medicine, Mansoura University; code number: MS.19.09.790.

Statistical analysis:

The Statistical Package for Social Science (SPSS) application for Windows was used to analyze the data (Standard version 21). The data's normality was initially evaluated using the one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data and median (min-max) for non-normal data. Significant variables were entered into a logistic regression model using the enter statistical technique in predicting the most significant determinants while controlling for any interactions and confounding effects. The threshold of significance for all of the above-mentioned statistical tests is set at 5%. When $p \leq 0.05$, the results were regarded significant. The lower the p-value, the more significant the findings.

RESULTS

Incidence of CVC-RI:

Out of the 114 hemodialysis catheters collected, 27 CVC-RI (23.7%) were documented with an incidence of 8.6 per 1000 CVC-days. Among these CVC-RI, 24 were LASI (21.1%, 7.7 per 1000 CVC-days) and 3 were ARBSI (2.6%, 0.9 per 1000 CVC-days).

Observation of hygienic measures:

During insertion all hygienic measures were applied because all catheters were inserted inside the operation room under complete aseptic precautions. While during maintenance compliance was as follows: applying hand hygiene (53.5%), wearing mask (57.9%), wearing gloves (100%), applying skin antiseptic (100%), using sterile drapes (0%). From the results obtained; poor hand hygiene compliance during maintenance and wearing masks had significant association with infection (table 1).

Table 1. Association between hygienic measure during maintenance of catheters and CVC-RI

	Infection group (n=27)	No infection (n=87)	Test of significance	p value
Mask during maintenance	11 (51.9%)	55 (67.8%)	$\chi 2$ =4.27	0.039*
Hand hygiene in maintenance	10 (70.4%)	51 (85.1%)	$\chi 2$ =3.85	0.049*

Demographic and clinical critaria of the study population:

One hundred patients were prospectively included in the study, 55 males and 45 females. Patients ranged in age from 5 to 17 years with a mean age of 10.74±3.65 years. The most commonly used site was jugular catheters (43%) followed by subclavian (30.7%) and femoral (26.3%). Maximum duration of catheter insertion was 46 days and minimum duration was 6 days. CVCs were removed in 23.7% of children for clinical suspicion of infection. 36.9% of catheters were removed due to thrombus formation leading to catheter occlusion so become nonfunctioning, and 39.4% of catheters were removed routinely after long period of insertion of the catheter to avoid infection. Regarding associated co-morbidity, almost third of patients (33.3%) had diabetes with renal disease. 10 patients (8.8%) were receiving immunosuppressive drugs. The remaining 66 patients (57.9%) had no associated co-morbidity. As shown in table 2, there was non statistically significant association between demographic data and infection. Infection occurred more in children with femoral catheters than those with subclavian or jugular catheters. We noticed no significant association between duration of insertion of catheters and the infection rate. Results revealed a significant association between infection and associated co-morbidity (diabetes and immunosuppressive drugs).

Table 2. Association between patients' characteristics and CVC-RI

	Infection group (n=27)	No infection (n=87)	Test of significance	p value
Age (years) Mean ± SD <10 y 10-15 y >15 y	 10.00±3.60 12 (44.4%) 12 (44.4%) 3 (11.1%)	 10.86±3.63 32 (36.8%) 39 (44.8%) 16 (18.4%)	t =1.08	0.283
Sex Male Female	 15 (55.6%) 12 (44.4%)	 48 (55.2%) 39 (44.8%)	χ^2 =0.001	0.972
Residence Rural Urban	 11 (40.7%) 16 (59.3%)	 35 (40.2%) 52 (59.8%)	χ^2 =0.002	0.962
Catheter site Jugular Subclavian Femoral	 8 (36.4%) 5 (22.7%) 9 (40.9%)	 35 (44.9%) 27 (34.6%) 16 (20.5%)	$\chi 2$ =11.94	0.003*
Duration of catheter Median (Min-Max)	20 (6-46)	23 (9-46)	Z= 1.61	0.106
Associated co-morbidity Yes No	 17 (63%) 10 (37%)	 31 (35.6%) 56 (64.4%)	$\chi 2$ =6.31	0.012*

*Significant p≤0.05

Isolated pathogens causing CVC-RI:

The majority of the pathogenic organisms were Gram-positive (77.8%), while Gram-negative organisms represented 22.2%. *S. aureus* was the most frequent organism detected as shown in table 3.

Table 3. Causative organisms causing CVC-RI among the study population

Causative organisms	LASI (n=24)	ARBSI (n=3)
Staphylococcus aureus	11 (45.8%)	2 (66.7%)
Coagulase negative *Staphylococcus*	4 (16.7%)	0 (0%)
MRSA	4 (16.7%)	0 (0%)
E-coli	3 (12.5%)	0 (0%)
Klebsiella pneumoniae	2 (8.3%)	1 (33.3%)

Antibiotic susceptibility pattern of the isolated organisms:

Antibiotic susceptibility pattern of isolated organisms is shown in tables 4 and 5. In Gram-positive organisms, imipenem and cefoxitin gave the best sensitivity results (81%). Half of organisms were resistant to cefuroxime and gentamycin. Eight (38.1%) of the detected organisms were multidrug resistant. 2 isolated *MRSA* were resistant to all antibiotics used including vancomycin (vancomycin resistant *S. aureus*). Antibiotic sensitivity test was repeated using linezolid and both isolates were susceptible to it. In Gram-negative bacteria: two-thirds of isolated bacteria were sensitive to cefotaxime, imipenem and amikacin. Most of isolated bacteria were resistant to gentamycin. Two (33.3%) of isolates were multidrug resistant.

Table 4. Antibiotic sensitivity pattern among Gram-positive organisms.

	The study group		
	Sensitive	Intermediate	Resistance
Amoxicillin-clavulanic	11 (52.4%)	-	10 (47.6%)
Ceftriaxone	12 (57.1%)	2 (9.5%)	7 (33.3%)
Cefuroxime	8 (38.1%)	2 (9.5%)	11 (52.4%)
Imipenem	17 (81%)	-	4 (19%)
Gentamycin	7 (33.3%)	3 (14.3%)	11 (52.4%)
Amikacin	12 (57.1%)	-	9 (42.9%)
Trimethoprim-sulfamethoxazole	10 (47.6%)	2 (9.5%)	9 (42.9%)
Cefoxitin	17 (81%)	-	4 (19%)
Azithromycin	10 (47.6%)	1 (4.7%)	10 (47.6%)
Vancomycin	12 (57.1%)	-	9 (42.9%)

Table 5. Antibiotic sensitivity pattern among Gram-negative organisms.

	The study group		
	Sensitive	Intermediate	Resistance
Amoxicillin-clavulanic	3 (50%)	-	3 (50%)
Piperacillin-tazobactam	3 (50%)	1 (16.7%)	2 (33.3%)
Cefepime	3 (50%)	-	3 (50%)
Cefotaxime	4 (66.7%)	-	2 (33.3%)
Ceftriaxone	3 (50%)	1(16.7%)	2 (33.3%)
Imipenem	4 (66.7%)	-	2 (33.3%)
Gentamycin	1 (16.7%)	1(16.7%)	4 (66.7%)
Amikacin	4 (66.7%)	1(16.7%)	1(16.7%)
Trimethoprim-sulfamethoxazole	2 (33.3%)	1 (16.7%)	3 (50%)
Vancomycin	3 (50%)	-	3 (50%)

Risk factors for CVC-RI

From results obtained, the risk factors for CVC-RI were as summarized in table 6. femoral catheters, associated co-morbidities as D.M and immunosuppression and poor compliance to infection control measures (hand hygiene and wearing masks) during maintenance of catheter were risk factors for CVC-RI.

Table 6. Logistic regression analysis for independent predictors of infection

	Univariate regression analysis			Multivariate regression analysis		
	P value	**OR**	**95% CI**	**P value**	**OR**	**95% CI**
Catheter site:						
Jugular (r)	-	1	(r)			
Subclavian	0.799	0.854	0.25- 2.8	0.788	0.843	0.24-2.9
Femoral	0.005*	4.484	1.6-12.7	0.008*	4.393	1.5-13.1
Associated co-morbidity:	0.014*			0.047*	2.72	1.01-7.3
Yes		3.07	1.25-7.5			
No (r)		1	(r)			
Hand hygiene in maintenance:	0.053			-	-	-
No		2.41	0.98-5.8			
Yes (r)		1	(r)			
Mask during maintenance:				-	-	-
No	0.042*	2.50	1.03-6.04			
Yes (r)		1	(r)			

(r); Reference group, OR; odds ratio, CI; Confidence interval

Outcome of CVC-RI:

All included patients received empirical therapy including vancomycin and amoxicillin-clavulanic acid and 22 patients received also cefepime. Empirical therapy was revised after antibiotics susceptibility results in infection. All patients recovered after receiving appropriate antibiotic according to antibiotic susceptibility.

DISCUSSION

Complications of HD access are common and lead to access-related procedures or medical interventions, which are a major cause of illness and death. Infectious complications are still a leading source of mortality among HD patients [11]. In our study, the rate of CVC-RI was 23.7% (21.1% LASI, 2.6% ARBSI) with an incidence of 8.6 per 1000 CVC-days (7.7 per 1000 CVC-days LASI, 0.9 per 1000 CVC-days ARBSI). While previously, in a study in Egypt, the rate of CVC-RI was 42.5% [12]. Sahli et al. [4] in Algeria found that the rate of CVC-RI was 22.4% (7.8% LASI, 14.6% ARBSI) with an incidence of 16.6 per 1000 CVC-days (5.8 per 1000 CVC-days LASI, 10.8 per 1000 CVC-days ARBSI). Schwanke et al. [13] reported a rate of infection of 9.1%. Another study identified that LASI incidence was 2.7 per 1,000 CVC-days and ARBSI incidence was 6.1 per 1,000 CVC-days [14]. This disparity could be attributed to factors as the notification criteria utilized, institutional policies for indwelling venous catheter care and maintenance, patients' adherence to guidelines, and the patient profile of hemodialysis patients. So, we underline the importance of distributing epidemiologic information on the occurrence of hemodialysis CVC-RIs. We noticed compliance to hygienic measures better than Sahli et al. who documented that the compliance of hygienic measures during insertion was as follows: hand hygiene (80%), wearing masks (0%), wearing gloves (90%), applying skin antiseptic (70%), using sterile drapes (70%) [4]. In hemodialysis unit in MUCH, nurses clean exit site of catheters with alcohol 70% or povidone-iodine 10% solution. This practice matches with what reported by McCann and Moore [15] who found that povidone-iodine reduced the risk of catheter-related bacteremia. Topical antibiotic ointments or spray was routinely applicated at the CVC exit site during maintenance. The use of topical antibiotic sprays or ointments has been linked to a 75–93% reduction in the risk of CVC-related infection [16]. Other studies demonstrated a reduction in infection rates when topical mupirocin has been applied to the exit site of catheters and nares [17-19]. Moreover, Sesso et al. [17] found a marked increase in *S. aureus* bacteremia when mupirocin was not used. Other studies that have demonstrated a reduced rate of skin colonization and bacteremia include catheters coated with chlorhexidine-silver sulfadiazine [20,21] or minocycline and rifampin [22]. While Saxena and Panhotra [23] made study that compared the efficacy of cefotaxime/heparin lock solutions with that of standard heparin lock solution in non-tunneled catheters. They

found a lower incidence of ARBSI in the patients treated with the combination lock. In our study the highest incidence of infection occurred in femoral catheters (40.9%). While the incidence in jugular catheters was 36.4% and in subclavian catheters was 22.7%. Similarly, Oto and Atkins [2] identified highest incidence of infection in femoral catheters. We found no significant association between duration of insertion of catheters and infection rate. This finding does not match with other studies who found that longer duration of CVC insertion in patients, the higher the risk of CVC-RI [4,12]. Our study revealed a significant association between CVC-RI and associated co-morbidity as diabetes and immunosuppression. This matched with previous studies [24-26]. The commonest micro-organism causing CVC-RI was *Staphylococcus*. This result matches with previous literature [27-30].

In a pediatric HD unit, ***Hymes et al.*** [31] described occurrence of a bacteremia outbreak of caused by *Enterococcus faecalis* in which no common source of *Enterococcus* could be established by culturing or serotyping. In another study conducted in Brazil, Gram-negative organisms were predominant in systemic infections while Gram-positive bacteria were predominant in local infections [14]. All patients with CVC received empirical therapy including vancomycin and amoxicillin-clavulanic acid and 22 patients received also cefepime. Empirical therapy was revised after antibiotics susceptibility results in infection. All patients recovered after receiving appropriate antibiotic according antibiotics susceptibility. The empirical antibiotics described in Sahli et al. were cefotaxime, vancomycin, imipenem, pristinamycin and metronidazole. In 82.3% of CVC-RI, recovery was obtained. 6 deaths had occurred: 3 deaths were due to non-infectious complications. The remaining 3 were from septic shock [4]. Prophylactic oral or parenteral antibiotics have been linked to a lower rate of ARBSI in the majority of studies [32]. However, their use is discouraged because of concerns that they encourage antibiotic resistance [33,34].

CONCLUSIONS

The rate of LASI in HD patients is relatively high but the rate of ARBSI is low. Most of detected organisms were Gram-positive (77.8%). Compliance to infection control measures is excellent during insertion but there are some defects regarding hand hygiene and wearing masks during maintenance. The risk factors for catheter related infections are femoral catheters, associated co-morbidity as D.M and immunosuppression and deficiencies in hand hygiene and wearing masks during maintenance of catheters. More compliance to hygiene measure with continuous training and education of health care worker for promotion of infection control measures are needed for decreasing hemodialysis CVC-RIs. Rational and judicious use of antibiotics by clinicians to decrease resistance is needed.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

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