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Original Article

Thrombolytic Therapy Using Urokinase for Management of Central Venous Catheter Thrombosis

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Purpose: The management of central venous catheters (CVCs) and catheter thrombosis vary among centers, and the efficacy of the methods of management of catheter thrombosis in CVCs is rarely reported. We investigated the efficacy of bedside thrombolysis with urokinase for the management of catheter thrombosis.

Materials and Methods: We retrospectively reviewed data from patients who had undergone CVC insertion by a single surgeon in a single center between April 2012 and June 2014. We used a protocol for the management of CVCs and when catheter thrombosis was confirmed, 5,000 U urokinase was infused into the catheter.

Results: A total of 137 CVCs were inserted in 126 patients. The most common catheter-related complication was thrombosis (12, 8.8%) followed by infection (8, 5.8%). Nine of the 12 patients (75%) with catheter thrombosis were recanalized successfully with urokinase. The rate of CVC recanalization was higher in the peripherally inserted central catheter (PICC) group (87.5%) than the chemoport group (50%). Reintervention for catheter-related thrombosis was needed in only 2.2% of patients when thrombolytic therapy using urokinase was applied. Age <60 years (P=0.035), PICC group (P=0.037) and location of the catheter tip above the superior vena cava (P=0.044) were confirmed as independent risk factors for catheter thrombosis.

Conclusion: Thrombolysis therapy using urokinase could successfully manage CVC thrombosis. Reintervention was rarely needed when a protocol using urokinase was applied for the management of CVC thromboses.

Key Words: Central venous catheters, Thrombosis, Urokinase-type plasminogen activator

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INTRODUCTION

Subcutaneously implanted ports (chemoport) and peripherally inserted central catheters (PICCs) are the most common vascular procedures for accessing the central venous system. These central venous catheters (CVCs) are used for the administration of chemotherapy, parenteral nutrition, and intravenous injections. In modern medicine, the need for these CVCs is increasing owing to the expansion of indications and patient's needs.

In many situations, CVCs are maintained for several weeks or months, and therefore, the management of complications associated with CVCs is an important issue. Catheter thrombosis is one of the most common com-

plication of CVCs that could need a secondary procedure. However, no uniform guidelines exist for the management of CVCs, and the methods to deal with catheter thrombosis vary among treatment centers. Moreover, the efficacy of the management of catheter thrombosis in CVCs is rarely reported. In our center, by using a protocol for the early diagnosis and management of catheter thrombosis in patients with CVCs, we aimed to investigate the efficacy of management for catheter thrombosis using urokinase at the bedside.

MATERIALS AND METHODS

We retrospectively reviewed data from patients who had undergone CVC insertion by a single surgeon in a single center between April 2012 and June 2014. In this study, a single type of chemoport system (Districath; Districlass Medical SA, Chaponnay, France) and a single type of PICC system (Turbo-ject; Cook Medical, Bloomington, MN, USA) were used. The diameter of chemoport was 8.5 Fr and PICC was 5 Fr. The procedures were performed under local anesthesia, and the patients were sedated selectively using midazolam. Intravenous cefazolin 1 g was administered for prophylaxis before the procedure, and all procedures were performed in aseptic conditions in an operation room. The access to target vessels was achieved under ultrasound guidance, and the location of the catheter tip was identified by using fluoroscopy after the procedure. The right internal jugular vein (IJV) was used primarily for the insertion of the chemoport, and if the access was not feasible, chemoports were inserted via the left IJV or through both subclavian veins (SCVs). The left basilic vein was used primarily for PICC insertion, and if it was not accessible, the left or right cephalic vein was used. We attempted to locate the catheter tip at the junction between the SVC and the right atrium (RA). In cases of malposition confirmed by fluoroscopy, we reattempted to determine their positions in the operating room. If repositioning of the catheter tip was not feasible, the procedure was completed after confirming catheter function in the operating room. After every procedure, the location of catheter tip was checked again using chest radiographs, and on the basis of these results, the locations from radiographs were categorized: the SVC, within the SVC, the junction of the SVC-RA, upper half of the RA and lower half of the RA.

The catheters were used from the day of procedure or the day after procedure. Before every procedure, the catheter was sterilized using povidone iodine, and the 22 G

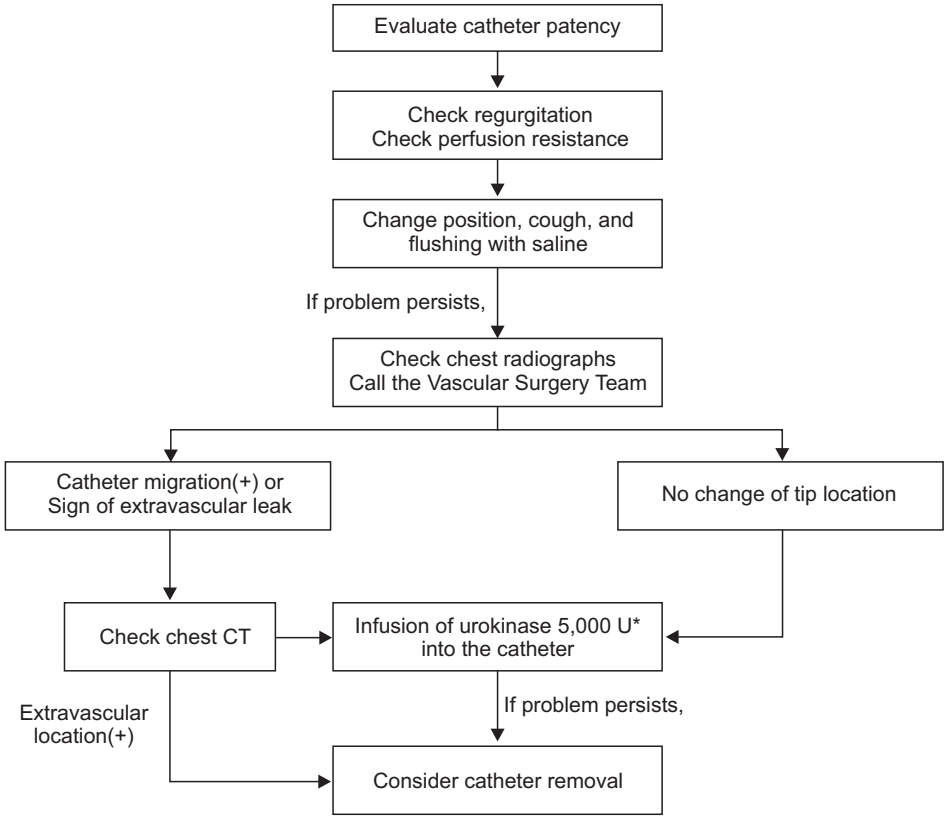

Fig. 1. Management protocol for catheter thrombosis. CT, computed tomography.

huber needle was inserted before using the chemoport. The patency of the catheter was confirmed by aspirating blood via the catheter before use.

Protocol for the management of CVCs: If the catheter malfunctioned, patients were encouraged to change positions and actively cough, and the catheter was flushed with normal saline. In case of continuous resistance during perfusion, or in case of no blood regurgitation via the catheter, chest radiographs were checked and the vascular surgeon was consulted. Because chest radiographs could not be used to confirm the location of the catheter tip within the intravascular space, chest computed tomography images were checked in cases with extravasation of fluid or suspicious findings of extravascular tip location. Catheter thrombosis was diagnosed when catheter malfunction persisted even after changes in position, active

Table 1. Patients' characteristics and procedural details

Characteristic	Total	Chemoport	PICC	P-value
Patients	126 (100.0)	84 (66.7)	42 (33.3)	
Male	68 (54.0)	42 (50)	26 (61.9)	0.206[a]
Age (y)	62.5±12.0 (29-88)	60.6±10.1 (34-82)	66.4±14.5 (29-88)	0.024[b]
Old age (≥60 y)	75 (59.2)	48 (57.1)	27 (64.3)	0.441[a]
Underlying disease				
Solid tumor[d]	96 (76.2)	73 (86.9)	23 (54.8)	<0.001[a]
Hematologic malignancy[e]	15 (11.9)	11 (13.1)	4 (9.5)	0.772[c]
Non malingnancy[f]	15 (11.9)	-	15 (35.7)	<0.001
Metastatic state	54 (42.9)	40 (47.6)	14 (33.3)	0.127[a]
BMI (kg/m^2)	22.4±4.18 (10-34.1)	23.0±3.66 (14.7-34.1)	21.1±4.88 (10-31.9)	0.027[b]
Obesity (BMI ≥25)	32 (25.4)	22 (26.2)	10 (23.8)	0.772[a]
Underweight (BMI <17)	23 (18.3)	10 (11.9)	13 (31.0)	0.009[a]
ECOG score (≥2)	31 (24.6)	11 (13.1)	20 (47.6)	<0.001[a]
Antiplatelet	20 (15.9)	15 (17.9)	5 (11.9)	0.449[c]
Anticoagulation	9 (7.1)	5 (6.0)	4 (9.5)	0.480[c]
Procedural details (n=137)				
Catheters	137 (100.0)	91 (66.4)	46 (33.6)	
Right side	87 (63.5)	76 (83.5)	11 (23.9)	<0.001[a]
Tip location				
Above SVC	8 (5.8)	2 (2.2)	6 (13.0)	0.017[c]
SVC	70 (51.1)	49 (53.8)	21 (45.7)	0.365[a]
RA junction	21 (15.3)	17 (18.7)	4 (8.7)	0.141[c]
RA upper 1/2	34 (24.8)	21 (23.1)	13 (28.3)	0.507[a]
RA lower 1/2	4 (2.9)	2 (2.2)	2 (4.3)	0.602[c]
Insertion site				
Internal jugular vein	90 (65.7)	90 (98.9)	-	
External jugular vein	-	-	-	
Subclavian vein	1 (0.7)	1(1.1)	-	
Cephalic vein	6 (4.4)	-	6 (13.0)	
Basilic vein	40 (29.2)	-	40 (87.0)	
Reoperation	11 (8.0)	7 (7.7)	4 (8.7)	1.000[c]

Values are presented as number (%) or mean±standard deviation (range).
PICC, peripherally inserted central catheter; BMI, body mass index; ECOG score, Eastern Cooperative Oncology Group performance status score; SVC, superior vena cava; RA, right atrium.
[a]Pearson's chi-square test, [b]Student t-test, [c]Fisher's exact. [d]Lung cancer 28 (22.2%), breast cancer 19 (15.1%), colorectal cancer 9 (7.2%), ovarian cancer 6 (4.8%), pancreatic cancer 5 (4.0%), stomach cancer 5 (4.0%), esophageal cancer 4 (3.2%), laryngeal cancer 4 (3.2%), cholangiocarcinoma 3 (2.4%), pertioneal cancer 2 (1.6%), other solid cancers 11 (8.8%). [e]Leukemia 9 (7.2%), lymphoma 4 (3.2%), other hematologic malignancies 2 (1.6%). [f]Pneumonia 3 (2.4%), short bowel syndrome 1 (0.8%), enterocutaneous fistula 1 (0.8%), polyneuropathy 1 (0.8%), others 9 (7.2%).

coughing, and flushing with normal saline. Cases of fluid extravasation or extravascular location of the catheter tip was excluded from the diagnosis of catheter thrombosis. When catheter thrombosis was diagnosed, 1 mL (urokinase 5,000 U) of urokinase solution (urokinase 20,000 U mixed with normal saline 4 mL) was infused into the catheter for 30 minutes for recanalization. If the catheter was not recanalized in the first attempt, the urokinase solution was infused again. If the catheter was not recanalized even after the second attempt, the catheter was removed. The protocol for the management of CVCs is summarized in Fig. 1. Heparin solution (100 U/mL) was dwelled into the catheter to prevent thrombus formation after every catheter use [1]. In addition, heparin solution was dwelled every 28 days in outpatients with chemoport and every 7 days in outpatients with PICC. In cases of patients who could not visit the hospital, nurses educated them the method of self injection.

Catheter-related infections were classified into local infections, catheter tip colonization, and catheter-related bloodstream infections (CRBSI). Local infection was defined as clinical or microbiologically proven infection at the catheter exit site: periorificial cellulitis, purulence, tunnelitis, and pocket infections (for totally implanted ports). Catheter tip colonization was defined as a positive semiquantitative culture in the intravascular catheter segment (>15 colony-forming units). CRBSI was defined as the isolation of the same strain from the catheter segment, a hub, or infusate and that from one or more peripheral blood cultures, as proven by restriction-fragment subtyping [2].

The mean follow-up duration of all patients was 128.8± 151.3 days (range, 1-813 days), and there was a significant difference in the follow-up duration between the chemoport group and PICC group (169.5±169.7 days [range 1-813 days] in the chemoport group vs. 48.3±40.4 days [range, 5-156 days] in the PICC group; P<0.001).

Statistical analysis were performed by using IBM SPSS Statistics for Windows, version 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

A total of 137 CVCs were inserted in 126 patients. Seven patients (7.7%) in the chemoport group and 4 (8.7%) in the PICC group underwent reintervention. The mean age of patients was 62.5±12.0 years (range, 29-88 years). Ninety-six patients (76.2%) had solid tumors, 15 had hematologic malignancies, and 15 (11.9%) had non-malignant diseases. Among the patients with cancer, 54 (48.6%) were diagnosed with metastatic disease. Of the total CVCs, 91 cases (66.4%) received chemoport and 46 (33.6%) received PICCs. Most of the chemoports (98.9%) were inserted into the right IJV, whereas most of the PICCs (87%) were inserted into the left basilic vein. The basic characteristics of the patients and procedures are described in Table 1.

Catheter-related complications of the procedures are

Table 2. Complications of central venous catheters

Complication	Total		Chemoport		PICC		P-value
	No. (%)	/1,000 catheter days	No. (%)	/1,000 catheter days	No. (%)	/1,000 catheter days	
Catheter related infection[a]	8 (5.8)	0.45	7 (7.7)	0.45	1 (2.2)	0.45	0.267
Catheter-related bloodstream infections	5 (3.6)	0.28	4 (4.4)	0.26	1 (2.2)	0.45	0.663
Catheter tip colonization	1 (0.7)	0.06	1 (1.1)	0.06	-	-	1.000
Pocket infection	2 (1.5)	0.11	2 (1.5)	0.13	-	-	0.551
Catheter thrombosis	12 (8.8)	0.68	4 (4.4)	0.26	8 (17.4)	3.60	0.021
Urokinase-success	9 (6.6)	0.51	2 (2.2)	0.13	7 (15.2)	3.14	0.007
Urokinase-failed	3 (2.2)	0.17	2 (2.2)	0.13	1 (2.2)	0.45	1.000
Extravascular leak	2 (1.5)	0.11	1 (1.1)	0.06	1 (2.2)	0.45	1.000
Patient induced removal	4 (2.9)	0.23	-	-	4 (9.7)	1.79	0.012
Catheter migration	1 (0.7)	0.06	1 (1.1)	0.06	-	-	1.000
Iatrogenic tearing	1 (0.7)	0.06	-	-	1 (2.2)	0.45	0.336
Pneumothorax	-	-	-	-	-	-	
Port exposure	-	-	-	-	-	-	

PICC, peripherally inserted central catheter.
[a]*Candida albicans* 2, coagulase-negative *Staphylococcus* 2, Methicillin-resistant *Staphylococcus aureus* 1, *Acinetobacter baumani* 1, *Candida tropicalis* 1, *Enterobacter cloacae* 1.
P-values by Fisher's exact.

Table 3. Univariate analysis of the risk factors affecting catheter thrombosis

Clinical characteristic	No catheter thrombosis	Catheter thrombosis	P-value
Old age (>60) (%)	78 (62.4)	4 (33.3)	0.05[a]
Obesity (BMI >25 kg/m^2)	31 (24.8)	5 (41.7)	0.300[a]
Underweight (BMI <17 kg/m^2)	23 (18.4)	2 (16.7)	1.000[a]
ECOG score ≥2	25 (20.0)	3 (25.0)	0.682[a]
Antiplatelet	21 (16.8)	1 (8.3)	0.690[a]
Anticoagulation	9 (7.2)	-	1.000[a]
Catheter-related infection	8 (6.4)	-	1.000[a]
Underlying disease			
Solid tumor	97 (77.6)	8 (66.7)	0.474[b]
Hematologic malignancy	13 (10.4)	2 (16.7)	0.621[a]
No malignancy	15 (12.0)	2 (16.7)	0.645[a]
Metastasis	53 (42.4)	6 (50.0)	0.762[a]
Type of catheter			
Chemoport	87 (69.6)	4 (33.3)	0.021[a]
Peripherally inserted central catheter	38 (30.4)	8 (66.7)	
Tip location			
Above SVC	5 (4.0)	3 (25.0)	0.023[a]
SVC	66 (52.8)	4 (33.3)	0.237[a]
RA junction	19 (15.2)	2 (16.7)	1.000[a]
RA upper 1/2	32 (25.6)	2 (16.7)	0.730[a]
RA lower 1/2	3 (2.4)	1 (8.3)	0.310[a]

Values are presented as number (%).
BMI, body mass index; ECOG score, Eastern Cooperative Oncology Group performance status score; SVC, superior vena cava; RA, right atrium.
[a]Fisher's exact, [b]Pearson's chi-square test.

Table 4. Multivariate analysis of the risk factors affecting catheter thrombosis

Clinical characteristic	Relative risk	Confidential range	P-value
Young age (<60 years)	4.352	1.108-17.095	0.035
Type of catheter (peripherally inserted central catheter)	4.185	1.088-16.094	0.037
Tip located above superior vena cava	6.092	1.052-35.276	0.044

P-values by linear logistic regression model.

summarized in Table 2. The most common catheter-related complication was catheter thrombosis (8.8%), followed by catheter-related infection (5.8%). Five cases of CRBSIs (3.6%), two of local infection (1.5%), and one of catheter tip colonization (0.7%) were included in the catheter-related infection group. There was no statistical difference in the incidence of catheter-related infections between the chemoport and PICC groups (P=0.985). However, the incidence of catheter thrombosis was significantly higher in the PICC group than in the chemoport group (P=0.021). When thrombolysis with urokinase was performed in cases of catheter thrombosis, 9 of 12 patients (75%) were successfully recanalized. The success rate of CVC clearance was higher in the PICC group than in the chemoport group (P=0.007). Catheter removal was needed in only 3 patients (2.2%) due to catheter thrombosis. In this period, no adverse events associated with urokinase were reported.

Two cases (1 each in the chemoport and PICC groups) had extravascular leaks. In this 1 patient in the chemoport group, fluid leak into the pleural space was found 1 day after insertion, and the catheter was removed promptly and closed thoracostomy was performed to drain the pleural fluid. In the 1 patient in the PICC group, soft tissue swelling around the catheter insertion site was noted, and the catheter was removed promptly. There were 4 cases of patient-induced catheter removal in the PICC group, and 1 case of iatrogenic catheter tearing in the PICC group. There were no cases of port exposure or pneumothorax.

A univariate analysis of risk factors affecting catheter thrombosis was performed, and results are presented in Table 3. Relatively young patients under 60 years had increased risk of catheter thrombosis (P=0.05), and the PICC group had a higher risk of catheter thrombosis than the chemoport group (P=0.021). In addition, when the tip of the catheter was above the SVC, the risk of catheter thrombosis was higher (P=0.023). However, obesity, underweight, performance status, administration of antiplatelets or anticoagulants and patient co-morbidities were not associated with catheter thrombosis (Table 3).

In multivariate analysis, all the significant variables in the univariate analysis were confirmed as independent risk factors for catheter thrombosis (age <60 years, P=0.035; the PICC group, P=0.037; catheter tip above the SVC, P=0.044) (Table 4).

DISCUSSION

Catheter thrombosis has been reported to have an incidence of 0.3%-28.3% [3-5]. Joks et al. [6] reported that risk factors for catheter thrombosis were exit-site infection and prior history of CVCs for chemotherapy. Saber et al. [7] reported that an implanted catheter-like chemoport had a lower risk of catheter thrombosis than external catheters, and that access to the jugular vein had lower risk of catheter thrombosis than access to the SCV. In addition, the risk of catheter thrombosis was higher when tips of CVCs were above the junction between the superior vena cava

and the RA.

No consensus has been reached regarding the relationship between age and catheter thrombosis. In most studies, age was not considered a risk factor for catheter thrombosis [7,8]. However, some studies have shown that the risk of catheter-related thrombosis increased in relatively young patients (age ≤60 years) [9]. Similarly, in this study, the risk of catheter thrombosis was higher in relatively young patients (age ≤60 years). The relationship between age and catheter thrombosis needs to be proven in further larger studies.

Earlier studies have reported the overall incidence of catheter-related infection as 0%-6.8% [10]. In this study, the overall rate of catheter-related infection was 5.8%, and this rate is relatively higher than those in previous reports. Several factors might have influenced the higher incidence of catheter-related infection in our study. First, all CVCs were inserted into patients as in-patients. The incidence of catheter-related infection was higher in the in-patient group than in the out-patient group [11]. Second, many patients included in this study were in the advanced stage of cancer (metastatic cancer, 42.9%). The impaired immune function in advanced cancer patients is very likely to have affected the incidence of catheter-related infection. Third, the performance status of the patients involved in this study was relatively low. The portion of patients with Eastern Cooperative Oncology Group performance status score (ECOG score) ≥2 was 24.6%. This reflects the fragility of the study population. Fourth, previous studies had used different definitions of catheter-related infections, and few studies had only included CRBSI [3,4,10]. In this study, all local infections, catheter-tip colonizations, and CRBSIs were considered catheter-related infections, and this would have contributed to the high rate of catheter-related infections. The incidence of catheter-related infection was reported to differ according to the type of CVC. Numerous prior studies on clinical experiences with PICC have suggested that PICCs pose a much lower risk of catheter-related infection than conventional CVCs placed percutaneously in the IJV or SCV, perhaps because of lesser dense bacterial colonization on the midarm than the sites used for conventional CVCs, such as the neck, upper chest, or groin [12,13]. However, recently, several meta-analyses have suggested conflicting results regarding the fact that the risk of catheter-related infection in PICCs are similar to those with conventional CVCs [10,14]. Chemoports are also known to have a low risk of catheter-related infections. As the catheter is completely underneath the subcutaneous layer, the risk of contamination is relatively lower with chemoports [15]. As in previous studies, this study did not show a statistically significant difference in the incidence of catheter-related infections between the PICC and chemoport groups [16].

Thrombolytic therapy for catheter thrombosis is known to be a safe and effective method for maintaining patency of CVCs [17,18]. Urokinase is a plasminogen activator that initiates fibrinolysis by converting plasminogen to plasmin. Previous studies have reported an 80%-96% success rate of CVC recanalization with thrombolysis [18-21]. Several factors, including type of thrombolytic drug, the method of administration, and the timing of administration can affect the success rate of CVC clearance. Haire et al. [20] suggested that, for the management of catheter thrombosis, alteplase was more effective in dissolving thrombi than urokinase. However, in this study, we used urokinase instead of alteplase because of costs incurred with alteplase and limitations in national insurance policies. Nevertheless, the overall success rate of CVC recanalization in our study was comparable to those of alteplase used in previous studies. This suggests that urokinase may be a good alternative to alteplase in terms of cost-effectiveness.

This study has several limitations. This was a retrospective study and the baseline characteristics were different between patients in the chemoport group and those in the PICC group. The proportion of patients who had chronic disease without cancer, short-bowel syndrome, or enterocutaneous fistulae was higher in the PICC group. Therefore, the PICC group included more patients who were underweight (body mass index <17 kg/m^2) and had low performance status (ECOG ≥2, Table 1). This study did not compare the chemoport and PICC groups, but the differences in patients' characteristics might affect the results of this study. The statistical power of our study was relatively low because of the small number of patients included. More conclusive results may be drawn using further studies with a larger sample size.

CONCLUSION

In this study, the overall incidence of catheter thrombosis was 8.8%. The incidence of catheter thrombosis was higher in the PICC group (17.4%) than in the chemoport group (4.4%). The overall success rate of CVC recanalization by thrombolytic therapy with urokinase was 75%, and the success rate was higher in the PICC group (87.5%) than in the chemoport group (50%). Reintervention due to catheter thrombosis was needed in only 2.2%. The risk factors for catheter thrombosis were age <60 years, abnormal catheter tip location (above the SVC) and the type of catheter (PICC).

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