Int J Clin Exp Med 2016;9(7):14670-14676
www.ijcem.com /ISSN:1940-5901/IJCEM0026041

Original Article

Peripherally inserted central catheter associated UEDVT in cancer patients: a retrospective review

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Received February 16, 2016; Accepted July 9, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Objective: Peripherally inserted central catheters (PICC)-related upper extremity deep venous thrombosis (UEDVT) is complicated and highly associated with malignancy in patients. The aim of this study is to evaluate PICC usage patterns and determinate if any clinical variables or high-risk technical variables are related to UEDVT in cancer patients with PICC. Methods: Clinical and technical variables were collected in 2861 cancer patients with PICC inserted from the medical record and tested for independent association with UEDVT by monofactorial and multivariable analysis. Risk factors were identified by logistic regression analysis and analyzed for the impact on UEDVT. Results: Diagnosis, chemotherapy and PICC insertion with real-time ultrasound guidance (or Seldinger technique) were investigated carefully, which significantly reduced the incidence of UEDVT ultrasound and exhibited abilities to dramatically reduce the incidence of PICC-related thrombosis ($P<0.05$). Conclusion: The ultrasound-guided method combined with Seldinger PICC as well as manipulation of technical variables can effectively reduce the incidence of UEDVT.

Keywords: PICC, UEDVT, cancer patients, risk, thrombosis

Introduction

Peripherally inserted central venous catheter (PICC) is non-tunneled medium- to long-term vascular via devices which are usually inserted into the deep veins of the upper extremities. PICC play an important role on cancer patients who need intravenous therapy. Upper extremity deep venous thrombosis (UEDVT) is the main complication of PICC. However, the actual symptoms of catheter-related deep vein thrombosis in cancer patients remain unclear, and reliable data related with risk factors of catheter-related deep vein thrombosis are still scarce. Hospital-related deep vein thrombosis (DVT), as one of the markers for the quality control in care, should be pay more attention. The Agency for Healthcare Research and Quality (AHRQ) has adopted postoperative pulmonary embolism (PE) and DVT as important indicators for evaluation of the safety of hospital patients. The study of AHRQ, including the veins of UEDVT (subclavian vein, axillary vein, jugular vein) cannot exclude thrombosis secondary to central venous catheter [1]. The purpose of this study is to evaluate PICC usage patterns and determinate if any clinical variables or high-risk technical variables were associated with UEDVT in cancer patients with PICC.

Materials and methods

We retrospectively reviewed 2861 cancer patients who had PICC inserted in the Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology between January 2011 and September 2012. Eligibility criteria included: 1) Pathologically diagnosed with cancer; 2) PICC placement. All PICC insertions were performed by a well-trained PICC expert team according to the manufacturer's instructions. The position of the tip of the catheter was confirmed with a chest x-ray. After PICC insertion, patients were instructed to put their hands and feet in warm water for 15 minutes and exercise fingers and wrist for 15 minutes twice a day. The follow-up period lasted until the end of treatment. Ultrasound was immediately performed if patient exhibited arm swelling, pain or any discomfort during the follow up period. The duplex ultrasonography criteria for the diagno-

Table 1. Demographic data of 2861 cancer patients

Characteristic		N (%)
Mean age (y)		50.08 ± 15.37
Gender	Male	1524 (53.3)
	Female	1337 (46.7)
Diagnosis	Head and neck cancer	261 (9.1)
	Thoracic cancer	863 (30.2)
	Breast cancer	260 (9.1)
	Abdominal cancer	520 (18.2)
	Genitourinary cancer	64 (2.2)
	Gynecologic cancer	302 (10.6)
	Hematological cancer	463 (16.2)
	Bone and soft tissue cancer	128 (4.5)

Continuous data are expressed as means ± SEM. Percent data reflect the total population of each group.

sis of UEDVT included direct signs (direct visualization of venous stenosis or occlusion the deep venous system) and indirect signs (amplitude attenuation, reduced flow rate, pulse transport deficiency, and significant stenosis or occlusion at the end of expiratory phase compared to the contralateral side). The survey log and data were collected by a professional PICC team. Medical records were obtained from the hospital information system (HIS). This study was approved by the Ethics Committee at Tongji Medical College, Huazhong University of Science and Technology.

Epidemiology

The incidence of PICC-associated UEDVT was calculated as the total number of PICC-associated UEDVTs of cancer patients, divided by the total number of PICCs placed during the same period. Meanwhile, patients receiving PICC insertions without UEDVT were considered as control.

Risk factors

The possible risk factors exposed between case group and control group were collected from medical history and statistically analyzed to evaluate clinical variables or high-risk technical variables and its impacts on the development of UEDVT in cancer patients with PICC.

The evaluation of clinical variables was consist of age, gender, diagnosis, body mass index (BMI), value of blood platelets and leukocytes, use of mannitol, cisplatin or steroid, subcutaneous injection of low molecular weight heparin (LMWH) and application of Mucopoly saccharide polysulphate cream after PICC insertion. Technical variables include catheter type, vessel catheterized (left or right, basilic, brachial, cephalic or median vein), use of ultrasound-guided or Seldinger technology, successful PICC placement or not (twice and more insertions, venous spasm, PICC adjustment of and clot formation were considered as unsuccessful PICC placement) and tip location of catheter (correct location determined by X ray was defined as in the superior vena cava at the level of anterior 3rd-4th intercostal space).

Statistical analysis

All statistical analysis was performed using the SPSS16.0 software (IBM Corporation, Somers, NY). The data of normal distribution were expressed as mean ± standard deviation (S.D.), while the data not meeting the normality assumption were expressed as medians and inter-quartile ranges. The clinical and technical variables were examined by univariate analysis. Categorical data (%) were compared using Chi-square test and quantitative data (means ± S.E.M.) were assessed by *t-test*. A logistic regression model was adopted to investigate the factors of UEDVT among patients exposed to PICC procedure. $P<0.05$ was considered statistically significant.

Results

Descriptive analysis

The demographic profile of 2861 cancer patients with PICC was showed in **Table 1**, including 1524 (53.3%) male patients and 1337 (46.7%) female patients, whose average age was 50.08 ± 15.37 years. The underlying diagnosis revealed head and neck cancer 261 (9.1), thoracic cancer 863 (30.2%), breast cancer 260 (9.1), abdominal cancer 520 (18.2), genitourinary cancer 64 (2.2), gynecologic cancer 302 (10.6), hematological cancer 463 (16.2), and bone and soft tissue cancer 128 (4.5). Among the 139 patients with UEDVT after PICC insertion, the median time to development of UEDVT was 10.00 days and the inter-quartile range of time was 22.00 days.

Single factor analysis

The clinical characteristics of the patients and the technical variables of PICC insertion were listed in **Tables 2** and **3**, respectively. The result

Table 2. Comparison of clinical variables association with UEDVT

Clinical variables	N	N UEDVT	UEDVT	x^2	*p* value
Gender				0.269	0.604
Male	1522	1445 (94.9)	77 (5.1)		
Female	1336	1274 (95.4)	62 (4.6)		
Diagnosis				21.578	0.003
Head and neck cancer	261	250 (95.8)	11 (4.2)		
Thoracic cancer	863	801 (92.8)	62 (7.2)		
Breast cancer	260	251 (96.5)	9 (3.5)		
Abdominal cancer	520	494 (95.0)	26 (5.0)		
Genitourinary cancer	64	61 (95.3)	3 (4.7)		
Gynecologic cancer	302	289 (95.7)	13 (4.3)		
Hematological cancer	463	455 (98.3)	8 (1.7)		
Bone and soft tissue cancer	128	121 (94.5)	7 (5.5)		
WBC				0.348	0.840
4.0-10.0*10^9/L	1852	1748 (94.4%)	104 (5.6%)		
<4.0*10^9/L	339	320 (94.4%)	19 (5.6%)		
>10.0*10^9/L	215	205 (95.3%)	10 (4.7%)		
PLT				1.032	0.597
100-300*10^9/L	1932	1824 (94.4)	108 (5.6)		
<100*10^9/L	108	100 (92.6)	8 (7.4)		
>300*10^9/L	369	351 (95.1)	18 (4.9)		
Mannitol				0.021	0.884
No	1663	1583 (95.2)	80 (4.8)		
Yes	1197	1138 (95.1)	59 (4.9)		
Cisplatin				8.388	0.004
No	2002	1920 (95.9)	82 (4.1)		
Yes	859	802 (93.4)	57 (6.6)		
Steroid				0.505	0.477
No	1069	1021 (95.5)	48 (4.5)		
Yes	1791	1700 (94.9)	91 (5.1)		
LMWH				15.557	0.000
No	1001	974 (97.3)	27 (2.7)		
Yes	1860	1748 (94.0)	112 (6.0)		
Hirudoid				2.477	0.116
No	420	406 (96.7)	14 (3.3)		
Yes	2441	2316 (94.9)	125 (5.1)		
BMI	2861	22.49 ± 3.23	22.73 ± 3.33	0.794	0.427
Age	2861	49.90 ± 15.49	53.52 ± 12.2	3.350	0.001

of single factor analysis suggested that statistically significant differences of thrombus formation were detected between two group of patients in different diagnosis (x^2=21.578, P=0.003), ultrasound-guided (x^2=12.301, P=0.000) and Seldinger techniques (x^2=29.734, P=0.000), use of cisplatin (x^2=8.388, P=0.004), injection of LMWH (x^2=15.557, P=0.000), and age (t=3.350, P=0.001).

Logistic regression analysis

The Logistic regression analysis (**Tables 4** and **5**) demonstrated that the Logistic regression equation was statistically significant (x^2=37.853, P<0.001). The variables was analyzed in the Logistic regression analysis, including diagnosis, chemotherapy, and the use of ultrasound (or Seldinger), and were statistically sig-

Table 3. Comparison of technical variables association with UEDVT

Technical variables	N	No UEDVT	UEDVT	x^2	*p* value
Catheter size					
3 Fr	11	10 (90.9)	1 (9.1)	1.354	0.508
4 Fr	2284	2169 (95.0)	115 (5.0)		
5 Fr	566	543 (95.9)	23 (4.1)		
Type of catheter				1.192	0.275
Three-way valve	2306	2189 (94.9)	117 (5.1)		
Open-ended	555	533 (96.0)	22 (4.0)		
Tip location of catheter				3.685	0.158
Normal	2145	2033 (94.8)	112 (5.2)		
Lower	506	484 (95.7)	22 (4.3)		
Deeper	210	205 (97.6)	5 (2.4)		
Side of insertion				1.431	0.232
Left	785	753 (95.9)	32 (4.1)		
Right	2076	1969 (94.8)	107 (5.2)		
Vessel catheterized				1.748	0.626
Basilic vein	2739	2604 (95.1)	135 (4.9)		
Brachial vein	93	90 (96.8)	3 (3.2)		
Median vein	11	11 (100.0)	0 (0.0)		
Cephalic vein	18	17 (94.4)	1 (5.6)		
Ultrasound-guided				12.301	0.000
No	228	206 (90.4)	22 (9.6)		
Yes	2633	2516 (95.6)	117 (4.4)		
Seldinger				29.734	0.000
No	158	136 (86.1)	22 (13.9)		
Yes	2703	2586 (95.7)	117 (4.3)		
Successful PICC placement				0.900	0.343
Successful	2706	2577 (95.2)	129 (4.8)		
Unsuccessful	155	145 (93.5)	10 (6.5)		

nificant associated with catheater-related thrombosis (P<0.05).

According to the analysis of regression coefficients, the Logistic regression equation can be listed as:

logitP=-2.478+0.450×Diagnosis (1)-0.119×Diagnosis (2)+0.255×Diagnosis (3)+0.186×Diagnosis (4)+0.020×Diagnosis (5)-0.972×Diagnosis (6)+0.243×Diagnosis (7)+0.400×Cisplatin-0.828×Seldinger.

Discussion

In 1823, Bouillaud *et al.* [2] firstly found that venous thromboembolism is a potential risk that exits in cancer patients. The pathogenetic mechanisms of cancer-induced thrombus are presented as follows: 1) Tumor cells can promote the blood coagulation by means of secretion of multiple tissue factors; 2) Microparticles (MP) or microvesicles shed from apoptotic cells has been proved to contain tissue factors associated with thrombus [3, 4]; 3) Stasis of the vein due to extrinsic compression of blood vessels by tumor or bet rest of cancer patient. Furthermore, cancer therapy can also contribute to the thrombus formation. For example, an incidence of UVDET in cancer patients receiving central venous catheterization for chemotherapy was 10%, which is lower than that reported by van rooden CJ *et al.* [5].

In the present study, the incidence of UVDET of cancer patients with PICC was 4.86%, which was consistent to the study by van rooden CJ [5]. In addition, thrombus risk factor is found to be associated with cancer diagnosis. Of all, the incidence of thrombus of thoracic tumor is highest (7.2%), and the next is bone and soft tissue tumor and abdominal tumor, the results of which are consistent with that of Bannink L [6] and Blo m JW [7]. Moreover, Age is generally acknowledged as one of thrombus risk factors. The increased risk paralleled with advancing age, which may be related to the decreased activity, increased underling disease, diminished functions of muscle pump or venous valve *etc*. Importantly, thrombus was emphasis as another critical factor in our study. Previous studies [8] have shown that overweight or obesity causes an increased incidence of thrombosis. However, we can not observe an association between obesity and thrombus, which may be due to cancer-associated wasting or demographic characters. In addition, our analysis also revealed that the risk of developing thrombosis in patients receiving cisplatin was 1.5 times higher than that

Table 4. Logistic regression analysis of different factors at risk for PICC-related UEDVT development

Parameter	Coefficient	SEM	Wald	*p* value	OR
Constant	-2.478	0.38	42.525	0.000	0.084
Diagnosis			15.895	0.026	
Diagnosis (1)	0.450	0.339	1.76	0.185	1.568
Diagnosis (2)	-0.119	0.46	0.066	0.797	0.888
Diagnosis (3)	0.255	0.371	0.473	0.492	1.291
Diagnosis (4)	0.186	0.669	0.077	0.781	1.205
Diagnosis (5)	0.02	0.423	0.002	0.963	1.020
Diagnosis (6)	-0.972	0.473	4.23	0.040	0.378
Diagnosis (7)	0.243	0.498	0.237	0.626	1.275
Cisplatin	0.400	0.191	4.400	0.036	1.492
US	-0.828	0.249	11.037	0.001	0.437

logitP=-2.058+0.425×Diagnosis (1)-0.127×Diagnosis (2)+0.217×Diagnosis (3)+0.178×Diagnosis (4)+0.005×Diagnosis (5)-0.972×Diagnosis (6)+0.239×Diagnosis (7)+0.410×Cisplatin-1.259×Seldinger.

Table 5. Logistic regression analysis of different factors at risk for PICC-related UEDVT development

Parameter	Coefficient	SEM	Wald	*p* value	OR
Constant	-2.058	0.386	28.443	0.000	0.128
Diagnosis			15.140	0.034	
Diagnosis (1)	0.425	0.340	1.565	0.211	1.530
Diagnosis (2)	-0.127	0.461	0.077	0.782	0.880
Diagnosis (3)	0.217	0.372	0.341	0.559	1.243
Diagnosis (4)	0.178	0.670	0.071	0.790	1.195
Diagnosis (5)	0.005	0.423	0.000	0.990	1.005
Diagnosis (6)	-0.972	0.473	4.223	0.040	0.378
Diagnosis (7)	0.239	0.500	0.229	0.632	1.270
Cisplatin	0.410	0.191	4.602	0.032	1.506
Seldinger	-1.259	0.254	24.505	0.000	0.284

Note: Diagnosis (1), Thoracic cancer; Diagnosis (2), Breast cancer; Diagnosis (3), Abdominal cancer; Diagnosis (4), Genitourinary cancer; Diagnosis (5), Gynecologic cancer; Diagnosis (6), Hematological cancer; Diagnosis (7), Bone and soft tissue cancer.

without receiving cisplatin. This risk could be triggered by cisplatin-related vascular toxicity, hypomagnesemia and increase of von Willebrand factor and procoagulant microparticles. It was also confirmed in a large retrospective analysis that all patients treated with cisplatin-based chemotherapy presented a high incidence of thrombus [9]. The incidence of UEDVT in patients receiving LMWH was 6%, while that without LMWH treatment was only 2.7% in this study. One explanation for this contradictory result is that LMWH was not only used for UEDVT prevention, but for the treatment. Therefore, it plainly can not be inferred that there is a statistically significant association between thrombosis and LMWH.

Grove and Pevec [10] described that larger diameter catheters could significantly increase the incidence of thrombus. By contrast, several other studies did not show any relationship between PICC diameter and thrombus. Consequently, using the smallest acceptable catheter of PICC based on the individual remains a principle of clinical practice [11]. Another risk to be reported is the tip location, while catheter tip placement in the distal superior vena cava was associated with a higher risk for DVT than tip placement at or just above the right atrium [12]. Following initial PICC placement in our study, the exact tip location was assessed with chest X-ray to confirm a correct position (defined as being in the superior vena cava or at the superior vena cava/right atrium junction) and any adjustments required were made, which precludes comparison between tip location and UEDVT.

PICC insertion with real-time ultrasound guidance is able to significantly reduce the incidence of UEDVT. By using ultrasound, the patients' veins can be assessed to select the correct type and size of cannula to improve insertion success rates, attenuates the number of unsuccessful attempts, and reduces the number of complications associated with catheter insertion [13]. PICCs placed in the antecubital fossa have a higher risk for mechanical phlebitis at the insertion site, as the patient bends his/her arm causing the catheter to move inside the vein and irritates the intima of the vein. Anstett and Royer found that PICCs placed above the antecubital fossa caused less catheter movement and in turn less sterile mechanical phlebitis and possibly less bacterial contamination [14]. Our results also corroborate the findings of another recent study by Stokowski *et al.* [15], indicating that PICC insertion by ultrasound guidance into veins in the upper arm gains a significantly lower rate of thrombosis. In addi-

tion, the use of modified Seldinger technique favored as it offers significant advantages, including targeting of the organ using a small needle, minimal vessel injury as well as a reduced incidence of UEDVT.

Conclusion

3 parts of Virchow's Triad, including Stasis, vascular injury and hypercoagulability (27), play important roles in the pathogenesis of thrombus formation and commonly exist in cancer patients with PICC. The use of LMWH for UEDVT prophylactic anticoagulant therapy remains controversial. For instant, according to the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), routine thrombo prophylaxis in cancer patients with indwelling PICC is not recommended. Prophylactic anticoagulant therapy with unfractionated heparin (UFH) or LMWH can improve the prognosis of cancer patients and reduce mortality based on the NCCN Clinical Practice Guidelines in Oncology. The ultrasound-guided method combined with Seldinger PICC can effectively reduce the incidence of upper extremity venous thrombosis. Vessel diameter should be assessed to select an appropriate size of PICC catheter prior to insertion, and change the puncture point from elbow to the upper arm can attenuate vascular intimal injury caused by the movement of PICC catheter at the puncture point. Appropriate functional exercise after PICC insertion, such as putting hands in warm water and other non-therapeutic measures, can also attenuate the risk of UEDVT incidence [11].

Limitations of the present study also need to be mentioned. As a retrospective review, some variables not observed previously can not be enrolled in the study. In addition, our data could only evaluate the factors in the cases of symptomatic UEDVT, but missed cases of asymptomatic thrombosis that was reported to have a higher incidence than that of symptomatic thrombosis. However, to our knowledge, our study is comprehensively summarize the clinical variables or high-risk technical variables associated with UEDVT in cancer patients with PICC. Further prospective study should be required to describe the impact of known and/or unknown risk factors on the development of UEDVT in cancer patients with PICC insertion.

Disclosure of conflict of interest

None.

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