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Heparinized Saline Flushed Catheter May Reduce Risk of Thrombosis in Cancer Patients Received Chemotherapy with Peripherally Inserted Central Catheter

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Abstract: Objective: This study investigated the effect of heparinized saline flushed catheter on preventing catheter-related thrombosis (CRT) among cancer patients received peripherally inserted central catheter (PICC) for chemotherapy. Background: CRT is a common and serious complication when using PICC, which is one of the most commonly used vascular access devices for drug infusion, intravenous nutrition, and chemotherapy. Methods: This prospective, paralled-group trial enrolled 300 cancer patients received chemotherapy who were randomly assigned to the intervention (n=150) or control (n=150) group. Besides the basic procedure of PICC combined with IC- ECG and B-mode ultrasound imaging, heparinized saline flushed catheters were used in the intervention group, while normal saline flushed ones were used in the control group. Hemorheology tests and tip sites measurements were used in outcome evaluation, and the incidences of CRT and other complications. In additions, thromboelastogram (TEG) were used to measure thrombus elastic before and one week after PICC. Results: 148 patients in the intervention group and 138 patients in the control group finished PICC and follow-ups, which indicating longer duration and more completion of PICC with better catheter tip positioning in the intervention group. Intervention subjects showed significant lower incidences of CRT and other complications (phlebitis, catheter blockage, catheter prolapse, and local infection) (P <.05). In additons, our proposed method may reduce CRT incidence via significantly improving blood circulation among patients received chemotherapy via PICC. Conclusion: Heparinized saline flushed catheter may increase chemotherapy completion quality via PICC, reduce the risk of catheter-related thrombosis complications, and reduce CRT incidence via improving blood circulation. Conclusions: This proposed method can be easily introduced to prolong the duration of the placement and improve the blood circulation of cancer patients received PICC.

Keywords: Heparinized, Saline, Flushing, Intracavitary, Electrocardiography, Catheter- Related Thrombosis

1. Introduction

Peripherally inserted central catheter (PICC) is commonly used for long-term drug infusion, intravenous nutrition, and chemotherapy. Compared with other drug delivery methods such as central intravenous catheter, PICC has advantages of longer application duration and fewer repeated puncture in preventing peripheral blood vessels injuries. Therefore, PICC is a preferred administration route for cancer chemotherapy [1-3]. However, as PICC is used, some complications and adverse events have been observed, such as catheter-related thrombosis (CRT), phlebitis, bleeding, etc., in which CRT is the most common and serious complication. Previous studies suggest that the incidence of symptomatic CRT and asymptomatic CRT is 2.0%~19.5% [4-7] and 25.2%~75% [7-9], respectively. CRT occurs in cancer patients who received chemotherapy, affecting efficacy, increasing treatment cost and psychological burden, and leading to poor prognosis including infection, pulmonary embolism, especially post-thrombotic syndrome [5-8, 10]. Unfortunately, proper strategy for preventing CRT after PICC catheterization is still unclear. Heparinized saline has an anticoagulant effect, which is used to prevent the formation of CRT after PICC catheterization [11-13], but its necessity and effectiveness are still controversial [14]. Some studies supported that it is reliable enough to position of PICC catheter guided with intracavitary electrocardiography (IC-ECG), which may reduce complications such as CRT [15-18]. In this study, we investigated whether Heparinized saline flushed catheter may prevent CRT formation after PICC catheterization guided with IC- ECG and ultrasound in various types of cancer patients.

2. Methods

2.1. Study Design and Participants

This prospective, parallel-group trial was conducted at the First Affiliated Hospital of Jinan University from July 2021 to Jun 2022. Cancer patients who received chemotherapy were randomly assigned to the intervention or control group. For insertion of the catheter, heparinized saline flushing combined with IC- ECG and B-mode ultrasound imaging were used in the intervention group, while normal saline flushing and B-mode ultrasound imaging were used in the control group. All participants signed a written, informed consent form before the start of the study. Inclusion criteria were all kinds of cancer patients in our hospital who received more than 2-week PICC catheterized through basilic vein, brachial vein, or cephalic vein for the first time. I n additions, participants aged more than 18 years old without abnormal coagulation function (including bleeding tendency, active bleeding, and thrombus-related diseases) and abnormal heart function. The baselines Karnofsky Performance Scale (KPS) need be more than 60. Criteria for exclusion were as follows: (1) Patients with skin inflammation, infection, and ulcer at the pre-puncture site before puncture; (2) T hose who are allergic to the chemotherapy; (3) History of superior vena cava syndrome and vascular surgery; (4) Patients with obvious thrombus or stenosis in the central vein; (5) Emergency catheterization on site; (6) Patients with severe hypoxemia, organ dysfunction, moderate and severe obesity, and heart disease; (7) Long-term use of anticoagulant and antiplatelet drugs is required; (8) Breastfeeding or pregnant women. Criteria for discontinuing participation in the study were as follows: (1) did not complete all investigations; (2) unable to continue participating in the study because of illness, pursuit of further study, maternity leave, etc.; and (3) voluntary withdrawal of informed consent during the study. The sample size was estimated based on $n = 4\times[(Z\alpha/2+Z\beta)2\times(p-q-)2]/(p0 - p1)2$, In which p0 is portion of control group, p1 is portion of intervention group, with a confidence interval of 95% (α=.05), statistical power of 90% (β=. 1) and comparison boundary value of [α, β]=10.8. According to this calculation, the minimum sample size for each group was determined to be 125. However, considering potential dropout and in order to ensure an adequate sample size, we increased the sample size of each group by 120% (n=300). The trial has been approved by the medical ethics committee of the hospital (approval number: KY-2022-256). Patients have signed the informed consent form.

2.2. Intervention

According to the traditional catheterization procedure, 100ml saline was used to immerse and flush the catheter, guide wire and Seldinger in the control group. However, 10 ml heparinized saline (10u/ml) was used to immerse and flush these tools in the intervention group. PICC catheterization was then guided by B-ultrasound under the positioning of IC- ECG in both groups. Both groups received the vision 5 ultrasound guidance system and the three-way valvular catheter with the specification of 4Fr produced by Bard Medical Technology Co., Ltd. The catheter tip should be inside the superior vena cava, the best position is the lower 1/3 segment of the superior vena cava and the CAJ point, which is defined as in-place, while outside the superior vena cava is defined as ectopic. I n-place rate of the catheter tip and catheter duration were recorded and analysed for PICC completion quality in both groups after one-week follow-up.

2.3. Outcome Measurements

Demographic information including age, sex, BMI, cancer type and complicating diseases were collected at baseline. Rates of completion in each group were recorded for primary outcome analysis. For safety analysis, according to the diagnostic criteria for CRT formation [19], enlarged venous lumen with a thrombus echo can be observed in the venous lumen via color Doppler ultrasound examination, in which blood vessels are not deformed with blood flows signal filling defect, detour, or no display when pressed by the probe. I n additions, thromboelastogram index, coagulation function index, and hemorheology index were used to evaluated patients before and 1 week after catheterization. T hromboelastogram was detected with CFMS thromboelastogram detector to determine the comprehensive coagulation index (CI), Ma value, α Angle, and K value, while activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen (FIB) levels were measured with a full-automatic hemagglutination analyzer (RAC-050, S henzhen Rayto Life Science Co., Ltd.). Plasma viscosity, hematocrit, and erythrocyte sedimentation rate (ESR) were measured with a full-automatic blood rheometer (LRY n7500b, Beijing Precil I nstrument Co., Ltd.).

2.4. Data Analysis

Data input and statistical analyses were performed using SPSS v21.0 software (IBM, Armonk, NY, USA). The χ 2 test or Fisher's exact test was used to assess intergroup differences, and the Mann–Whitney U test or Wilcoxon signed-rank test was used to evaluate intergroup differences. Continuous and nonnormally distributed data were described as the median and interquartile range (25%–75%), while categorical variables are described as frequencies (%). The threshold for significance was set to P <.05 for all tests.

3. Results

3.1. Characteristics of the Study Population

A total of 300 cancer patients received chemotherapy with PICC were enrolled at our hospital. Patients were randomly divided into control group (n=150) and intervention group (n=150). There were no statistically significant differences in age (P =. 196), sex (P =.729), BMI (P =.489), catheterized vein (P =.462), cancer type (P=.743) or underlying diseases (P =.754) between the two groups (Table 1). According to the details on patient recruitment and follow-up (Figure 1), 148 patients finished all the PICC in the intervention group, while 138 ones finished in the control group.

Table 1. *Summarizes the clinical characteristics of the patients in the two groups.*

	Intervention group (n= 150)	Control group (n= 150)	P value
Sex [n (%)]			0.729
Male	72 (48.0)	69 (46.0)	
Female	78 (52.0)	81 (54.0)	
Age (years)	56.29±7.06	57.46± 8.52	0. 196
BMI [n (%)]	22.19±2.06	22.35± 1.94	0.489
Catheterized vein [n (%)]			
Basilic vein	119 (79.3)	124 (82.7)	0.462
Brachial vein	31 (20.7)	26 (17.3)	
Cancer type [n (%)]			0.743
Gastrointestinal cancer	51 (34.0)	59 (39.4)	
Gynecological cancer Respiratory	32 (21.3)	32 (21.3)	
cancer Head and neck cancer	33 (22.0)	27 (18.0)	
Underlying	34 (22.7)	32 (21.3)	
Diseases [n (%)]			0.754
Diabetes	31 (20.7)	28 (18.7)	
Hypertension	54 (36.0)	50 (33.3)	
COPD	16 (10.7)	14 (9.3)	
No other underlying diseases	49 (32.6)	58 (38.7)	

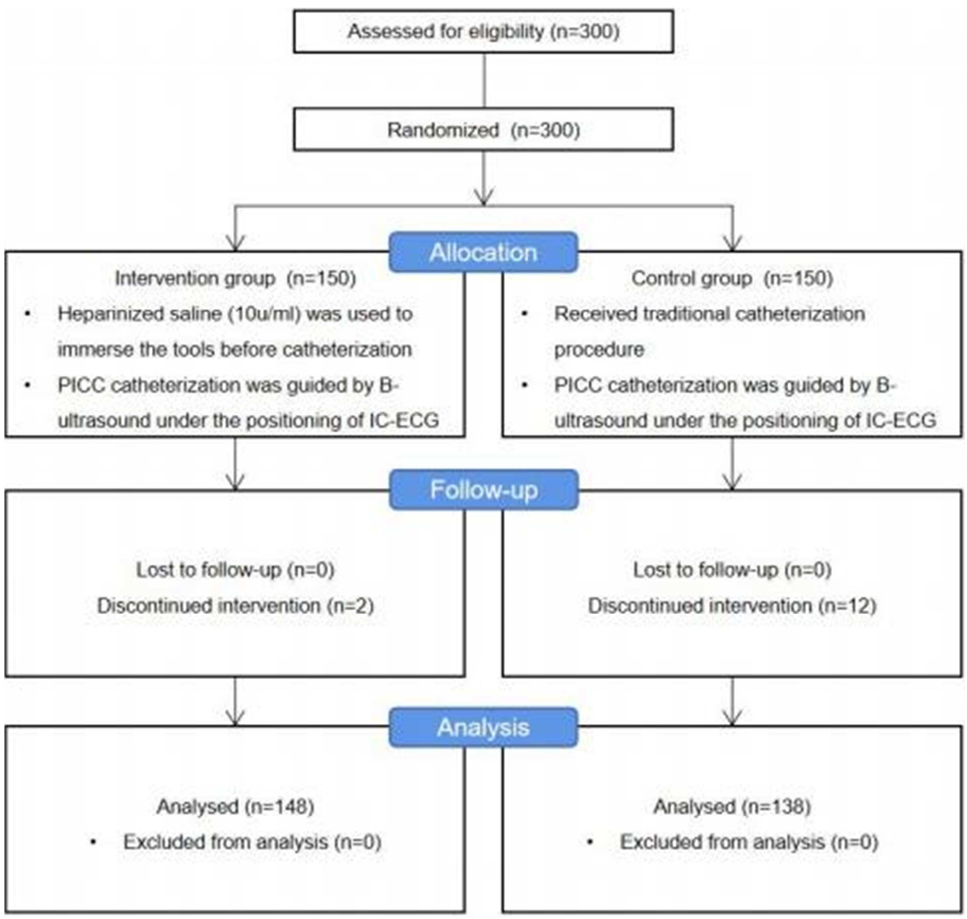

Figure 1. *Flow diagram at each stage of the trial.*

The PICC completion rate was significantly higher in the intervention group than that in the control group (P<0.05), while the in-place rate of catheter tip and use time showed same difference between these two groups (Table 2).

Table 2. *Comparison of catheter tip in-place rate and catheter use time between two groups.*

	n	Catheter tip in-place rate (%)		Catheter use time (d)
		In-place	Ectopic	
Intervention group	148	146 (98.65)	2 (1.33)	126.47± 17.36
Control group	138	126 (91.30)	12 (8.70)	89.85± 14.49
t/χ2		8.491		19.834
P		0.004		<0.001

3.2. Catheter-Related Thrombosis and Other Complications

The incidence of catheter-related thrombosis or bleeding in the intervention group was lower than that in the control group (P < 0.05). There was no significant difference in the incidence of phlebitis, catheter blockage, catheter prolapse, and local infection between two groups (Table 3).

Table 3. *Comparison of catheter-related thrombosis and other complications between the two groups n (%).*

	n	Catheter-relat ed thrombosis	Phlebitis	Catheter occlusion	Catheter prolapse	Local infection	Oozing of blood
Intervention group	148	0 (0.00)	1 (0.68)	0 (0.00)	3 (2.03)	0 (0.00)	31 (20.95)
Control group	138	42 (30.43)	4 (2.90)	2 (1.45)	8 (5.80)	4 (2.90)	47 (34.06)
χ2		48.837	0.814	0.503	2.359	2.280	4.435
P		<0.001	0.367	0.478	0. 125	0. 131	0.035

3.3. Thromboelastogram and Coagulation Function Index

The thromboelastogram index, APTT, Pt, and FIB levels showed no significant statistical differences before catheterization between the two groups. After catheterization, there were significant differences in thromboelastogram, APTT, Pt, and FIB levels between the two groups (P < 0.05) (Table 4).

Table 4. *Comparison of thromboelastogram indexes and coagulation function indexes between the two groups before and after catheterization (x ±s).*

		n	CI index	MA value (mm)	α angle (°)	K value (min)	APTT (s)	PT (s)	FIB (g/L)
Before catheterization	Intervention group	150	1. 18±0.39	59.86±6.25	61.74±5.26	2.25±0.32	27.59±5.63	12.68±2.07	2. 17±0.75
	Control group	150	1.26±0.43	61. 13±5.44	62.59±6.41	2.30±0.35	27.26±6. 14	12.47± 1.96	2.24±0.79
	t		1.688	1.877	1.256	1.681	0.485	0.902	0.787
	P		0.923	0.062	0.210	0.093	0.628	0.368	0.432
After catheterization	Intervention group	148	2.41±0.47	65.42±7.08	66.34±6.28	1.47±0.25	26.07±4. 12	11.95± 1.43	2.45±0.82
	Control group	138	3. 16±0.56	71.97± 8.82	73.75±7.73	0.94±0.29	24.94±3.58	11.04± 1.28	2.80±0.89
	t		12.564	7.093	9. 112	16.953	2.536	5.807	3.542
	P		<0.001	<0.001	<0.001	<0.001	0.012	<0.001	<0.001

3.4. Hemodynamic Indexes

There were no significant differences in plasma viscosity, hematocrit, and between the two groups before catheterization, while significant differences in plasma viscosity, hematocrit, and ESR were showed between the two groups after catheterization (P<0.05) (Table 5).

Table 5. *Comparison of hemodynamic indexes between the two groups before and after catheterization (x ±s).*

		n	Plasma viscosity (mPa ·s)	Hematocrit (%)	ESR (mm/h)
Before catheterization	Intervention group	150	3. 16±0.52	39.59±4. 18	31.49±4.52
	Control group	150	3.09±0.47	39.06±3.72	32.06±4. 17
	t		1.223	1. 160	1. 135
	P		0.222	0.247	0.257
After catheterization	Intervention group	148	3.76±0.58	43. 16±4.41	36.24±5.80
	Control group	138	4.21±0.64	46.24±4.75	41.38±6.68
	t		6.381	5.820	7. 116
	P		<0.001	<0.001	<0.001

4. Discussion

Our study introduced heparinized saline flushed catheters in PICC catheterization among the cancer patients for the first time, which indicating lower incidence of CRT in patients suffered from multiple cancer types. As a result, longer PICC duration and more PICC completion was found in the intervention group, consistent with previous studies [11-13, 15-18, 20]. T hree main factors including hypercoagulability, slowing blood flow rate, and vascular endothelial injury were reported to increase CRT formation during PICC catheterization [13]. In order to prevent vascular endothelial injury, IC- ECG combined with ultrasound is used to real-time monitoring for accurate catheter tip positioning before catheterization. To reduce blood viscosity and improve blood circulation, low-molecular heparin sodium is used to flush catheters before catheterization for its anticoagulant properties [11-13]. In our study, all the complications and adverse events of PICC with different catheters were investigated, whose results showed that the incidences of phlebitis, catheter occlusion, and catheter prolapse were lower in the intervention group. Therefore, our proposed method may prevent both post-catheterization CRT and other catheter-related adverse events among cancer patients. As a more accurate and rapid coagulation function detection, thromboelastography can be used to monitoring the overall coagulation process in the dynamic process, consist with coagulation system initiation, fibrin clot formation, and fibrinolysis [21-22]. In this study, we also found that there' re significant differences in thromboelastography indexes and other coagulation function indexes, which suggest our proposed method may decrease the risk of CRT formation and improve coagulation status of patients. Notably, the fibrinogen (FIB) level, an index of coagulation function, was reported as an independent risk factor in CRT formation after PICC catheterization [23]. In this study, the FIB level was lower in the intervention group, while APTT and Pt levels in the intervention group were significantly higher after catheterization. Therefore, the coagulation function of the control subjects was significantly higher after PICC catheterization. Previous study reported that post-PICC catheterization coagulation status monitoring with thromboelastography could predict and prevent CRT [24]. I n our study, all the index on thromboelastography were significantly different between groups after catheterization with different cathethers. I n additions, the decrease of blood flow rate is also one of the essential factors in CRT formation [13]. Reflecting fluidity, adhesiveness, deformability, and coagulability of blood, hemorheological index is associated with erythrocyte aggregation and venous thrombosis [25, 26] In our study, all the blood rheology index were significantly lower in the intervention group after PICC, suggesting that our method may reduce CRT incidence via significantly improving blood circulation. This study had some limitations. Patients who enrolled this study received various chemotherapy, and the different impact of these regimens were not investigated. These warrants further exploration in future studies to determine the other influence factors.

5. Conclusion

Traditional PICC assisted with IC- ECG and B-ultrasound may present the risk of CRT and other related complications among cancer patients, which needs to be improved. Heparinized saline flushing combined with IC- ECG and B-mode ultrasound imaging may reduce these risks and improve the coagulation status and blood circulation, contributing to longer duration of catheter use and lower treatment cost. This new method should be integrated into further research and clinical promotion.

In addition to improving traditional method, heparinized saline flushing needs to be combined with IC- ECG and B-mode ultrasound imaging. Our proposed method may not only be effective in preventing post-catheterization CRT in cancer patients but also have applied potency in preventing other related complications and catheter-related adverse events, which deserves further research and promotion in the future. Regarding the levels of thromboelastography indexes and coagulation function indexes t, our proposed method may alter the coagulation status to decrease the incidence of CRT.

Conflict of Interest

The authors declare that they have no competing interests.

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