Received:
01 August 2017

Revised:
24 October 2017

Accepted:
07 November 2017

<https://doi.org/10.1259/bjr.20170560>

Cite this article as:

Koo CM, Vissapragada R, Sharp R, Nguyen P, Ung T, Solanki C, et al. ABO blood group related venous thrombosis risk in patients with peripherally inserted central catheters. *Br J Radiol* 2018; **91**: 20170560.

FULL PAPER

ABO blood group related venous thrombosis risk in patients with peripherally inserted central catheters

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Objective: To investigate the association between ABO blood group and upper limb venous thrombosis (VT) risk in patients with peripherally inserted central catheters (PICC).

Methods: Single centre retrospective cohort study. A cohort of patients who underwent PICC insertion from September 2010 to August 2014 were followed up for symptomatic VT presentations diagnosed by ultrasound. Blood group status was identified from hospital information systems.

Results: 2270 participants had 3020 PICCs inserted. There were 124 cases of symptomatic VT, an incident rate of 4% [95% confidence interval, CI (3–5%)]. Univariate analysis adjusting for the clustered sample showed that having chemotherapy, two or more previous PICCs, a larger catheter size, a diagnosis of cancer and having a blood group B were all associated with an increased risk of a VT. In the

multivariate analysis, PICC diameter, cancer diagnosis and blood group B were all independently associated with increased risk of VT.

Conclusion: Patients undergoing PICC insertion with a blood group B appear to have a higher risk of VT, independent of risks attached to the PICC procedure and cancer diagnosis. Without any existing guidelines for PICC-related VT, this investigation creates a platform for further research to be conducted in order to establish guidelines.

Advances in knowledge: Previous studies investigating VT risk associated with blood group status related to large heterogeneous populations. In this article, we look at patients specifically with PICC, which reduces the heterogeneity in the cohort. In addition, due to the substantial number of patients enrolled, we had a chance to perform multivariate analyses with statistical significance.

INTRODUCTION

Peripherally inserted central catheters (PICC) are a well-established and commonly performed procedure for long-term intravenous access, with the first journal article describing its risks and benefits as early as 1975.¹ PICC use has recently increased worldwide due to increased patient satisfaction and provision of out of hospital care.² One of the major complications of PICCs is venous thrombosis (VT). Symptomatic VT affects up to 5% of patients with a PICC.^{3,4} Risk factors for PICC-associated VT include PICC diameter, diagnosis of cancer and high catheter to vein diameter ratio.^{3,5}

Non-O blood group has been demonstrated to increase the risk of VT in multiple studies.^{6–9} A meta-analysis by

Dentali et al found patients with a non-O blood group had twice the odds of developing a VT [Odds Ratio 2.08; 95% confidence interval (CI) (1.83–2.37); $p < 0.00001$].¹⁰ This is thought to be due to higher levels of glycoproteins such as von Willebrand factor and factor VIII.¹¹ Further, this risk appears to be higher in patients with a malignancy. Previous research in patients with glioma indicates that blood group AB has a significantly higher hazard ratio of 9.4 ($p \leq 0.0001$) for thrombosis compared to blood group O.^{12,13} Despite a significant proportion of the population with a potentially higher risk of VT due to blood group, to date, there is no literature examining this in patients with PICCs. We aim to determine the association between blood group and risk of upper limb VT in patients with a PICC.

METHODS AND MATERIALS

This single centre retrospective cohort study was approved by the Human Research Ethics Committee at the Royal Adelaide Hospital, Adelaide, Australia. The requirement for informed consent was waived because of its retrospective nature. Data were collected from the Hospital Information System, Radiology Information System and electronic medical record program Open Architecture Clinical Information System.

The Radiology Information System was used to access PICC insertion information including reason for insertion and catheter size. The electronic medical record program Open Architecture Clinical Information System was used to collect patient demographics, co-morbidities and blood type. Doppler ultrasound results were accessed to identify cases of symptomatic thrombosis. Patients were followed for 1 year post PICC insertion to allow inclusion of delayed PICC-associated upper limb VT.

Outcome measure

The primary outcome measure was symptomatic VT. Cases of symptomatic thrombus were included if sonography determined occlusive venous thrombosis in the vein the PICC was inserted (cephalic, basilic or brachial) or extension to more proximal deep veins (axillary or subclavian veins).

Data analysis

Descriptive statistics were used to present information about the study population in the form of percentages and counts. Chi-squared tests were used to compare groups on baseline information. The association between blood group and risk of thrombus was analysed using a log binomial generalized linear model (GLM). It was known that participants would be in the data set more than once, hence the GLM was adjusted for clustering. Each potential predictor variable was first entered into a univariate log binomial GLM. Variables that were associated with VT at the 0.05 level in the univariate model were included in the multivariate analysis. Statistical analyses were undertaken using the Stata 14 statistical package, Stata Corp., College Station, TX.

Study population

All adult (18 years or older) patients who had undergone PICC insertion in the Radiology Department at the Royal Adelaide Hospital between 1 September 2010 and 31 August 2014 were included. Each patient's record was followed up for 1 year post insertion. We decided on 12 months as follow up because at our institution, the longest time a PICC is allowed to remain is 12 months after the initial day of insertion. Patients were excluded if blood type was not recorded in hospital information systems.

Power analysis

Based on a chi-squared test with two-sided significance set at 0.05 and 80% power, a sample size of 1121 subjects in each group was required, assuming that 50% of the sample is non-O. The rate of VT in the blood group O was assumed to be 2% in the blood group O and 3.9% in the non-O blood group.

Table 1. PICCs inserted—patient and PICC characteristics

Characteristic		<i>n</i>	%
Gender	Female	1299	43
	Male	1721	57
	Total	3020	100
Age (years)	18–29	147	5
	30–45	352	12
	46–65	1147	38
	66+	1374	45
	Total	3020	100
Reason for PICC	Chemotherapy	810	41
	IV Antibiotics	864	43
	Other	249	12
	Multiple	72	4
	Total	1995	100
Previous PICCs	0	2269	75
	1–2	648	22
	≥3	100	3
	Total	3017	100
Arm side	Right	2003	76
	Left	646	24
	Total	2649	100
Catheter size	4 Fr	1623	64
	5 Fr	656	26
	6 Fr	109	4
	7 Fr	165	6
	Total	2553	100
Cancer diagnosis	No	2005	66
	Yes	1015	34
	Total	3020	100
Rhesus factor	Negative	504	17
	Positive	2514	83
	Total	3018	
Blood group	O	1332	44
	A	1196	40
	B	362	12
	AB	130	4
	Total	3020	100

PICC, peripherally inserted central catheter.

RESULTS

Study population

There were 2270 participants with 3020 PICCs inserted. Clinical characteristics of the PICC insertions are shown in Table 1. Missing data were excluded in the analysis. There was a slightly higher percentage of males compared to females, and nearly half of the patients

were over 65 years. A third of participants had a cancer diagnosis (solid tumour or haematological malignancy). The most common primary indications for PICC insertion were intravenous antibiotics and chemotherapy. Blood group O was the most common blood group in the sample (44%), followed by blood group A (40%), blood group B (12%) and blood group AB (4%).

Venous thrombosis

There were 124 cases of symptomatic venous thrombosis, yielding an incidence rate of 4% [95% CI (3–5%)]. These comprised of 38 deep vein thrombosis (31%), 41 superficial vein thrombosis (34%) and 42 (35%) affecting both the deep and superficial vasculature. The median time from PICC insertion to venous

thrombosis diagnosis was 15 days (range 1–348 days; interquartile range 7–35 days).

Patient factors and venous thrombosis

There was a similar distribution of age, gender, previous number of PICCs, side of PICC insertion and blood group in those who developed VT and those who did not (Table 2). Those who had a cancer diagnosis, a larger catheter and received chemotherapy had significantly more incidence thrombosis.

Univariate analysis adjusting for the clustered sample showed that having chemotherapy, two or more previous PICCs, a larger catheter size, a diagnosis of cancer and having a blood group B

Table 2. Patient factors and venous thrombosis

Characteristic		Venous thrombosis					
		Yes (<i>n</i> = 124)		No (<i>n</i> = 2896)		Total (<i>n</i> = 3020)	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	Sig ^a
Gender	Female	49	4	1250	96	1299	0.422
	Male	75	4	1646	96	1721	
Age (years)	18–29	8	5	139	95	147	0.319
	30–45	13	4	339	96	352	
	46–65	55	5	1092	95	1147	
	>66	48	3	1326	97	1374	
Reason for PICC	Chemotherapy	67	8	743	92	810	<0.001
	IVAB	23	3	841	98	864	
	Other	8	3	241	97	249	
	Multiple	1	1	71	99	72	
Previous PICCs	0	92	4	2177	96	2269	0.760
	1–2	29	4	619	96	648	
	≥3	3	3	97	97	100	
Arm side	Right	97	5	1906	95	2003	0.125
	Left	22	3	624	97	646	
Catheter size	4 Fr	42	3	1581	97	1623	<0.001
	5 Fr	37	6	619	94	656	
	6 Fr	13	12	96	88	109	
	7 Fr	12	7	153	93	165	
Cancer diagnosis	N	42	2	1963	98	2005	<0.001
	Y	82	8	933	92	1015	
Rhesus factor	Negative	22	4	482	96	504	0.751
	Positive	102	4	2412	96	2514	
Blood group	O	44	3	1288	97	1332	0.067
	A	50	4	1146	96	1196	
	B	22	6	340	94	362	
	AB	8	6	122	94	130	

IVAB, intravenous antibiotics; PICC, peripherally inserted central catheter.

^aBased on X².

Table 3. Univariate and multivariate modelling of patient risk factors for venous thrombosis

Risk factor		Venous thrombosis					
		Univariate analysis			Multivariate analysis		
		RR	95% CI	Sig ^a	RR	95% CI	Sig ^b
Gender	Female	1.00					
	Male	1.16	0.78–1.71	0.468			
Age (years)	18–29	1.00					
	30–45	0.68	0.26–1.74	0.422			
	46–65	0.88	0.41–1.89	0.744			
	>66	0.64	0.30–1.38	0.257			
Reason for PICC	IVAB	1.00					
	Chemotherapy	3.11	1.95–4.94	<0.001	1.13	0.38–3.35	0.827
	Other	1.21	0.54–2.66	0.642			
	Multiple	0.52	0.07–3.81	0.521			
Previous PICCs	0–1 Previous PICCs	1.00					
	≥2 Previous PICCs	1.64	1.03–2.63	0.039	1.17	0.73–1.91	0.508
Arm side	Right	1.00					
	Left	1.42	0.91–2.23	0.126			
Catheter size	4 Fr	1.00					
	5 Fr	2.18	1.40–3.40	0.001	1.61	1.00–2.58	0.046
	6 Fr	4.61	2.47–8.59	<0.001	2.93	1.53–5.63	<0.001
	7 Fr	2.81	1.51–5.25	0.001	1.60	0.83–3.07	0.155
Cancer diagnosis	N	1.00					
	Y	3.86	2.63–5.66	<0.001	3.60	2.26–5.75	<0.001
Rhesus factor	Negative	1.00					
	Positive	0.93	0.59–1.46	0.750			
Blood group	O	1.00					
	A	1.27	0.85–1.88	0.272	1.41	0.90–2.13	0.139
	B	1.84	1.12–3.03	0.031	2.13	1.19–3.82	0.011
	AB	1.86	0.93–3.71	0.076	1.44	0.66–3.17	0.360

were all associated with an increased risk of a VT (Table 3). In particular, those with blood group B had 1.84 times the risk of VT compared to those with blood group O.

In the multivariate analysis, PICC diameter (6 Fr), cancer diagnosis and blood group B were all independently associated with an increased risk of VT.

DISCUSSION

Summary of results

This study found that blood group B was a significant risk factor for developing VT in patients with a PICC compared to blood group O. Patients who had blood group B had more than a two-fold increased risk compared with blood group O. This association remained true even after adjusting for cancer diagnosis and catheter size, which are powerful predictors in their own right. Blood group A and AB were also seen to be a higher risk

compared to blood group O but this was not statistically significant [relative risk (RR) 1.41 and 1.44, respectively] in multivariate analysis. However, it is important to note that because only 4% of the patients in this study had blood group AB, statistical significance was more difficult to achieve.

This study is the first to investigate the association between blood group and VT risk in patients with a PICC. Our results are comparable to previous literature¹⁰ with a heterogeneous group of hospital patients, which found those with non-O blood groups had approximately a two-fold risk of VT. However, this study did not identify whether a vascular access device was in place. In previous research with glioma patients, Streiff et al found higher hazard ratios in blood group A (2.7) and AB (9.4) compared to blood group O.¹² Unfortunately, the risk of VT associated with blood group B could not be reported in this study because it violated proportional hazards ratio assumption. As 65% of the participants in the study by

Streiff et al had undergone chemotherapy, it could be assumed that they did have a vascular access device in place, although this was not reported. Our results differ for those participants with blood group A and AB, which may be due to the smaller and more homogenous sample size (glioma patients).

The results of the present study support similar studies in cancer patient populations. The incidence of VT in previous research in cancer patients with a PICC was 15% (36/237 patients) in Anh et al¹⁴ and 7.8% (39/498 patients) in Tran et al.¹⁵ This is compared to an incidence of 8.8% (82/1015 patients) in our study. A cancer diagnosis was associated with an almost four-fold risk of VT [RR 3.86; 95% CI (2.63–5.66)] in the present study, which was much higher than a similar study in cancer patients [OR 1.95; 95% CI (1.01–3.76)].¹⁶ Although caution is required when comparing rate ratios and odds ratios, the incidence of DVT in the unexposed population is less than 10% in this study, making OR and RR appropriate to compare.¹⁷

The risk attributed to cancer as a diagnosis remained similar in both univariate and multivariate analyses in our study [RR 3.86; 95% CI (2.63–5.66) and RR 3.6; 95% CI (2.26–5.75), respectively]. Patients with 6 Fr catheters had a three-fold increase in thrombosis rates, which has been reported in previous research.^{16,18} The relative risk associated with blood group B and cancer did not change after adjustment. In fact, the ratio was higher in multivariate vs univariate analysis [RR 2.13; 95% CI (1.19–3.82) vs RR 1.84; 95% CI (1.12–3.03)]. This is perhaps the strongest indicator that blood group B may be an independent risk factor that likely compounds the risk of VT in patients with other risk factors.

Theoretically, cancer is known to increase thrombosis due to hypercoagulability and endothelial damage. Reasons for increased risk of thrombosis with certain blood groups are yet to be fully uncovered. Some may be related to levels of procoagulant factor VIII, vWF, increased platelet aggregation and thrombus formation, which are higher in certain blood groups.⁶ The link between the transcriptional upregulation and synthesis of these factors, however, has not been established.¹³

Clinical implications

The aim of this study was to determine whether blood group status was a risk factor for VT in patients with a PICC. However, even though our results have confirmed blood group B as an independent risk factor for VT, the clinical implications may be ambiguous. These patients still need venous access for treatment, and it is not clear how this risk could be reduced. Chemical prophylaxis (low molecular weight heparin or fixed dose warfarin) is not effective in reducing VT rates in cancer patients with a range of central vascular access devices including PICCs.¹⁹

Luo et al reviewed weekly ultrasounds in cancer patients with a PICC and described encouraging results using a screening strategy. The asymptomatic thrombosis rate was noted to be

48.8% (62/127), 85% (53/62) of which were diagnosed within the first week.²⁰ Our study found that the majority of VT occurred within the first month of PICC insertion (median time to venous thrombosis was 15 days). While these results are comparable to Luo et al, the studies differ in design and sample size. What can be agreed is that the highest risk is within the first few weeks. There are no current guidelines or even consensus on screening and/or treatment of upper extremity VT. Although it remains to be seen whether screening is recommended, we hope that this study adds to the existing knowledge and opens the forum to establish clinical guidelines. Upper limb VT causes discomfort, interrupts treatment, which has large cost implications and may be associated with increased morbidity and mortality.¹⁴ Regular screening is not currently performed at the institution where the research took place. Although ultrasound is non-invasive, it can carry a large cost implication if used as a screen tool. Hence, further research could investigate screening in high-risk patients such as those with blood group B, cancer, or 6 Fr catheters *in situ* in a prospective study design.

Limitations

Patients' anticoagulation status was not collected in this study, which could influence their risk of VT. Furthermore, other factors contributing to increased thrombosis risk, such as past medical history (other than cancer), mobility and stage of cancer were not recorded. Also, patients who had previous VT were not excluded because these patients would still need PICC for the indication (antibiotics, chemotherapy etc.). It is a limitation that is difficult to control because patients with VT are more likely develop another. However, if these were excluded in the study, it could potentially underestimate the risk levied by the notable risk factors. Instead, multivariate analyses were conducted to reduce overestimation of the impact of the noted variables.

Duration of PICC line was another variable that was outside the scope of this investigation due to unavailability of medical records for this large cohort of patients. Many patients would have the PICC inserted at a tertiary centre, but have it removed at their local doctors or by the district nurses' service. Finally, the large amount of missing data for some variables did decrease the power of our analyses.

CONCLUSION

In addition to confirming cancer and PICC size (6 Fr) as a risk factor for VT in patients with a PICC, our study has determined that blood group B is an independent risk factor for VT. Further research is needed to determine the efficacy of screening in this patient population to reduce the risk of VT in those requiring a PICC and extend this study to lower limb VT.

ACKNOWLEDGMENTS

The authors would like to thank Melita Cummings MN and Debra Matthews for data collection and technical assistance.

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