Full Title: Impact of arm selection on the incidence of PICC complications: Results of a Randomized Controlled Trial

Short title: Impact of arm selection on incidence of PICC complications

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Previous submission:

Manuscript was rejected by JVIR based on our study design which included grouping of the complications and selection of certain controlled variable. They wanted us to add a variable (hypercoagulability status) but this was not measure throughout the study as this is not something we measure part of routine care.

Reviewers did not agree with our choice and definitions of complications and said we should have screened for CR-DVT instead of only symptomatic and only select a few complications. The study was not design to target specific complications. Our study aimed at being representative of the wide range of patients with various co-morbidities and a reflection of the practice in a large university teaching hospital with multiple inserters and a large group of nurses. The reviewers of JVIR would have

wanted a study with more variable controlled. We were not in a position to revisit the study design after completion of the study.

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Conflict of interests: Ms. Paquet reports non-financial support from Vygon, personal fees and non-financial support from Benson Dickinson, personal fees and non-financial support from 3M, non-financial support from Smiths Medical, outside the submitted work. Dr. Boucher reports personal fees and non-financial support from BTG (Therasphere), outside the submitted work. Dr. Valenti reports personal fees and non-financial support from BTG (Therasphere), personal fees and non-financial support from XACT robotics, personal fees from Guerbet, personal fees from Carestream, personal fees and non-financial support from Siemens, personal fees from Covidien, outside the submitted work. Dr. Lindsay has nothing to disclose.

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Abstract and key words

Introduction: To determine if right arm PICCs experienced fewer complications while controlling for gender, hand dominance, history of malignancy, dwell time and catheter size.

Methods: This was an intention to treat randomized controlled trial conducted in an academic medical center on two different sites between September 2012 and September 2015. All patients older than 18 years or age without known history of previous central line, contraindication to the use of a specific arm or hospitalized in the intensive care unit regardless of coagulation status, were considered for the study. Participants were randomized to the left or right arm group and were followed until catheter removal. Data collected included: PICC characteristics, insertion details, gender, arm dominance, history of malignancy, reason for insertion/removal, incidence of a complication and total dwell time. One-tailed hypothesis testing using a univariate logistic regression with Odds ratio calculation was used to analyse the results. There were 202 patients randomly assigned, totalling 7657 catheter-days; 103 patients to the right side group and 99 patients to the left side group.

Results: Participants in both groups were statistically equivalent for right handedness, gender, oncologic status, average dwell time and total catheter days. The overall incidence of complications on the right side was 23% vs 34% on the left side, confirming the hypothesis that right sided insertions led to fewer complications (p=0.046). The risk of a complication was reduced by 40% with right-sided insertion (OR 0.58 (CI: 0.31-1.09).

Conclusion: This study indicated fewer complications with right-sided insertion irrespective of hand dominance.

Key words: PICC Peripherally inserted central catheter, arm, functional laterality, intention to treat analysis, catheter occlusion, accidental removal,

Introduction

Peripherally inserted central catheters (PICCs) are widely used to enable administration of intravenous medications or for blood samplings. The insertions of PICCs remains the most common procedure performed by interventional radiologists (1). These catheters are also routinely placed by nurses at the bedside(2, 3). PICCs are associated with complications ranging from medical adhesive-related skin injury (MARSI), catheter dislodgment, occlusion or more severe complications such as catheter related deep vein thrombosis (DVT) and central line associated blood stream infection (CLABSI)(4, 5). Recently, initiatives to decrease the risk of complications have focused primarily on reducing the incidence of catheter related DVT (6, 7) and care and maintenance guidelines aimed at reducing the incidence of CLABSI and occlusions (8, 9).

Although optimal tip position in the central vein(10), use of ultrasound to direct the venotomy, and optimal puncture position in the upper arm(11), are associated with a reduction in complication rates(12), there is lack of evidence regarding arm selection. Nonetheless, vascular access specialists generally favor the right side as demonstrated in several studies (13-18).

Since 2011, several studies on specific PICC complications have been published. According to Marjenon et al. (19), there are more catheter related DVT in left-sided PICCs, however, other authors did not observe a difference in the incidence of symptomatic catheter related DVT (15, 20, 21). One large prospective observational cohort study of medical/hematological oncology patients, reported a 1.62-fold increased risk of CLABSI with right-sided PICC (22) but a study with a smaller group of patients did not confirm this result (17).

Because of these conflicting results, the authors conducted an intention-to-treat prospective randomized controlled trial to test the hypothesis that right arm

PICCs would lead to fewer complications resulting in a change or an unplanned increase in the level of care while controlling for gender, hand dominance, history of malignancy, dwell time and catheter size.

Methods

This study was approved by the research and ethic board of the authors' institution. Because of the paucity of available data on complication rates based on side of insertion at the time of protocol development, the sample size was decided based on convenience and the authors' experience of first PICC inserted annually. Between September 25, 2012 and September 25, 2015, 203 patients were enrolled from two different sites of a tertiary university teaching institution and randomly assigned to an insertion either on the right or on the left regardless of their arm dominance. A computerized random sequence generator was used to attribute side of insertion. The side of insertion was placed in a sealed envelope and numbered in sequence. Upon randomization, the envelopes were opened in order to determine the side of insertion. All patients over 18 years of age referred for a PICC insertion were invited to participate in the study by the interventional radiologist on site. Exclusion criteria were as follows: known history of previous condition preventing use of an arm (eg. dialysis fistula, stroke/paralysis), known history of previous central catheterization, participation in an active stage of a trial, unable to follow instructions, pregnant or nursing female subjects, or hospitalized in the intensive care unit at the time of recruitment. Informed consent was obtained from all participants.

To control for technique of insertion and optimal tip placement, all PICC insertions were carried out in the interventional radiology suite, under fluoroscopy and ultrasound guidance, by an interventional radiologist. The following PICC's were inserted during the study: ProPICC (Medcomp, Harleysville, PA, USA) and Turboflo

(Cook Medical, Bloomington, IN, USA) double lumen 5Fr and single lumen 4Fr (Table 2). Both brands of PICCs are reverse tapered. Tapered PICCs were introduced at the authors' institution in the early 2000 to reduce the incidence of bleeding and associated dressing changes.

Catheter tips were placed at the level of the cavoatrial junction, 2 vertebral bodies below the carina +/- 0,75 vertebral body as described by Baskin (23). This location was assessed using fluoroscopy at the time of insertion. The skin entry site was in the middle third (upper part) of the upper arm, away from the antecubital fossa. At the time of insertion, the catheter was stabilized with a sutureless securement device (Statlock®) and the inserter left an average of 2 cm (0cm to 4.5cm) of catheter outside of the skin to reduce the amount of tapered catheter inside the vessel. Leaving 2 cm of the taper outside has been the practice for 5 years, as recommended by a vascular access coordinator, to ease dressing change and to reduce blood flow impairment by the larger size of the taper of the catheter used (24). Vein measurements were not recorded as part of the study. Because of the size of the vessel, the basilic vein was preferentially targeted; if unavailable the brachial was the next choice. Single lumen PICCs were inserted by default, unless there was a specific indication for two lumens(25, 26).

Bedside nurses performed care and maintenance during the hospital stay and home care nurses provided care if the patient was discharged home with the device. The initial dressing consisting of the sutureless securement device and a dry dressing was replaced by a transparent dressing combining catheter stabilization and protection (Tegaderm®IV Advanced, 3M®) 24 hours post insertion. Follow up data was obtained by direct communication with the patient, chart review and discussion with the treating physician or nurse. Follow up was done on a weekly

basis and continued as long as the catheter was in situ. Patients were considered as having completed the study at the time of removal of the catheter.

All data collection and analysis was performed with an intention-to-treat approach. This was defined as all randomized patients with a PICC successfully inserted in the central venous circulation. Data including PICC and patients characteristics, presence of a complication leading to a change or an unplanned increase in the level of care (e.g. radiologic imaging, change in dressing regimen, initiation of antibiotics or anticoagulation, reinsertion of the catheter or another vascular access device) (table 1), and dominant arm according to patient report were collected. The hypothesis that right-sided insertions had fewer complications than left-sided insertions led to one-tailed hypothesis testing using an univariate logistic regression with odds ratio calculation, 95% confidence intervals and p-values. A p-value <0.05 was considered significant. Catheter size, dominant arm, history of malignancy and dwell time were inserted into the model to correct for their effect. All analyses were performed using the R Statistical Language® Software, version, 3.2.2.

The incidence of at least one complication was used in the logistic regression. It was decided to analyse complications globally because, major complications, such as CLABSI and catheter related DVT or minor complications such as MARSI, occlusion, and catheter dislodgment result in a change in care, a catheter reinsertion, or cause a delay in treatment (27-31). All of these complications can significantly affect the patient, the health care providers or the hospital system. Their definitions are outlined in Table 1.

A total of 203 patients were randomized (102 from hospital site A and 101 from hospital site B). One patient was excluded from the analysis as the PICC could not be inserted at the cavoatrial junction due to a stenosis of the subclavian vein.

The data on 202 patients, totalling 7657 catheter days, was used for the statistical analyses (see Table 2). Participants in both groups were statistically equivalent for right handedness, gender, oncologic status, average dwell time and total catheter days. Only 3 out of 202 patients were lost to follow-up. Lost to follow-up was determined after unsuccessful attempts to contact the patient or absence of documentation of the removal in the electronic patient record at the time of study closure, at least 265 days after study enrolment. Thus, reason and date of removal was not obtained for 3 patients (Table 3). The information concerning the dominant hand was missing for 3 other patients. Missing data, because of the intention-to-treat paradigm, was treated as follows: total dwell-time in 3/202 was estimated to be the mean of all known data (38 days). For the data missing for the complications, in 3/202: one case inserted on the right, counted as having a complication to bias toward the null hypothesis and 2 cases inserted on the left, counted as no complication to bias toward the null hypothesis. For the three cases where arm dominance was missing, this was randomly generated using a 12% chance of being left handed as documented in the literature(32).

Results

PICCs were inserted for antibiotic administration 45% of the time, followed by chemotherapy (30%), parenteral nutrition (14%), lack of other venous access (5%) and long-term IV therapy (4%), equally distributed in both left and right group (table 2).

A large number of complications were observed during the study. Twenty-nine percent of the catheters had at least one complication, leading or not to removal. Seventy-four percent of the PICCs were removed because therapy was completed (78% of right-sided vs 69% of left-sided) (Table 3). The incidence of one or more than one complication occurred in 24/103 (23%) of right arm insertions and 34/99

(34%) of left arm insertions. Table 4 describes the incidence of the individual complications noted during the study. The most common complications were catheter dislodgment (17/202, 8.4%) and occlusion (17/202, 8.4%). Reinsertion secondary to these complications was necessary in 16 out of 17 dislodgments (94%) and 11 out of 17 (65%) occlusions.

Using a logistic regression model and one-sided hypothesis testing, the hypothesis that PICCs inserted in the right arm experienced fewer complications (p=0.046) was confirmed. The calculated OR of 0.581(0.306-1.086) suggests that an insertion on the right side lowers the risk of a complication by 40% (Table 5).

Discussion

The results confirmed the hypothesis that right-sided PICCs lead to fewer complications. However, given the borderline p-value, it seems reasonable to believe that the effect of the side of insertion is quite small. Other variables, such as diagnostic of malignancy or tip position, have been well described as increased risk factors and likely account for more of the variance. For this matter, prior to performing insertion, it is essential to ensure appropriate assessment of the patients. If a PICC is deemed the most appropriate device, both sides should be assessed for vein caliber, ease of access of the vein and appropriate location of the puncture site on the upper arm. These elements of the insertion probably play a more important role in the risk of complication. Patients requiring PICCs are vulnerable and heterogeneous in their diagnosis, past medical history, treatment plan and vascular integrity. According to Moureau, the high prevalence and significance of intravenous device placement calls for a reliable access to ensure delivery of the prescribed treatment plan(33). It is necessary to ensure the most appropriate device placement with safe management of that device from hospital admission right up to

discharge(33). Incidence of complications resulting in a change or increase in the level of care was statistically analysed as a group because they impact the clinical course of the patient and represent a burden on the health care system. However, they will be discussed individually to allow comparison with published literature.

The results indicate a high incidence of complications: 34% for left-sided insertion vs 23% for right-sided insertion and an overall complication rate of 29%. Similar to this study, LeRoyer, reported a rate of 36% of complications including occlusion, accidental removal, venous thrombosis, infectious complications and cutaneous problems in a study of 200 PICCs inserted in an teaching hospital for an heterogeneous population(34). Catheter dislodgment was frequent with an incidence of 8.4% (2.22/1000 catheter days). This is comparable to Bellesi(35) and LeRoyer who respectively reported a rate of 2.3/1000 catheter days and 7% for accidental removal (34, 35). Catheter dislodgment or migration of the catheter are problematic as they often lead to reinsertion of the catheter (7.4% of study participants) and re-insertion becomes more challenging with every occurrence (36). Additionally, catheter dislodgment and migration lead to catheter reinsertion, venous thrombosis, early termination of therapy or delay in treatment(37). In the study population, a higher percentage of catheter dislodgment or migration in the left arm insertion group (right 9/103 (8.7%) vs left 12/99 (12%)) was noted. The activity that precipitated the catheter loss (i.e. dressing change or activity of daily living) was not identified. One possible explanation that can be offered for the increased rate of left-arm catheter dislodgment/migration was that the patients, predominantly right-handed, were more aware of the catheter in their dominant arm resulting in careful arm movement and improved catheter care, although this remains to be demonstrated. .

Occlusion occurred in 8.4% of the catheters. Reported occlusion rates vary greatly depending on the authors. Some authors will only report complete occlusion

(absence of blood return and inability to infuse), whereas others will report partial occlusion (resistance during infusion with or without brisk blood return) and withdrawal occlusion (no resistance while infusing but absence of blood return). The presented occlusion rate includes all three types of occlusions, as they all have clinical impact. For this reason, it is difficult to compare the results to previously published studies. For example, Leroyer et al.(34) reported 8% of removals due to obstruction of the catheter and an overall rate of obstruction of 20% without a precise definition of the obstruction. Overall in this study, more occlusions in the left-sided insertion group (right 6/103 (5.8%) vs left 11/99 (11.1%)) were observed and more occlusions in the left side insertion group required reinsertion (right 4/103 (3.9%) vs left 7/99 (7%)). One possible explanation is the anatomy of the vessel when the insertion is performed from the left (38). Moreover, the total length of the catheter is greater when the insertion is performed from the left, increasing resistance to infusion and flushing and also potentially creating more reflux into the catheter with body movement(39). This difference may have contributed to the observed increase in occlusions.

Catheter related DVT is one of the most severe complications in PICCs. In this study, 9/202 (4.5%) patients developed a symptomatic catheter related DVT with arm swelling or pain and radiological confirmation (right: 4/103 (3.8%) vs left: 5/99 (5%). These numbers are comparable to published literature (40). Similarly to Liem et al.(20), Sperry et all(21) and Aw et al.(15), no difference was observed between the left and ride-sided PICCs. However, also similar to previous publications, a much higher incidence of catheter related DVT was observed in the patients with a malignancy diagnosis (9.8% vs 2.1%) (13).

CLABSIs also occurred more frequently in the patients with a malignancy diagnosis, where all 4 CLABSIs occurred in patients with a recent history of

malignancy (solid and hematological tumors). Contrary to Mollee et al. (22), the authors did not observe more CLABSIs in the right arm even when looking specifically at oncology patients. In fact, more CLABSI occurred in the left-sided PICCs (3:1). However, due to the small number of patients and events, the authors cannot make a conclusion about the side of the insertion in relation to the incidence of CLABSI.

Limitations

A limitation of the study is that patient recruitment was somewhat challenging, with some patients refusing to participate, as they wanted to decide in which arm the catheter would be inserted instead of random allocation. Additionally, to control for the increased risk of complications associated with patients who have received multiple PICCs (36), the authors only included patients who were receiving their first PICC. Results may have varied with a wider population with fewer exclusion criteria. Moreover, patients hospitalized in the intensive care unit were excluded as well as patients with contraindications that would have restricted arm choice such as the presence of a pacemaker or paralysis. Therefore, these results may not be applicable to all patients requiring a PICC. In addition, because of the low incidence of specific complications, to evaluate these individually or to evaluate specific factors that affect complication rates would necessitate a much larger number of patients. Future research on individual complications such as catheter dislodgment, occlusion and patients with history of multiple PICCs is required.

This study suggested that right-sided insertions were associated with fewer complications leading to a change or an increased in the level of care at a statistically significant level ($p=0.046$) regardless of hand dominance. The incidence of at least one complication was greater in the left-sided insertion group (34% vs 23%). It is pertinent to analyse the incidence of complications globally as they all

have an impact on the care provided to the patient or on the financial burden on the health care system even though the long term impact of complications such as accidental removal and occlusion can be minimal on patient health.

The authors recognize that the results obtained are on the limit of statistical significance and that in an individualized clinical context, they suggest that the side of insertion impacts for a small proportion of the incidence of a complication. This highlights the importance of including all other controllable variables that will reduce the risk of a complication which includes: a careful assessment of both sides to ensure selection of a vein of appropriate caliber and depth, selection of an easily accessible vessel, insertion in the appropriate area of the upper arm and optimal tip location. Based on the results, in the absence of a contraindication and veins of equal quality, the authors suggest favoring the right side.

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Table 1. Complication definitions and SIR classification		
	Definition	SIR Classification(27)
Catheter dislodgment:	Accidental removal or movement (greater than 0,5cm) that resulted in the loss of function of the catheter(28).	B. Nominal therapy, no consequence, includes overnight admission for observation only
Catheter related deep vein thrombosis (CR-UEDVT)	Visualization of an intravascular thrombus, incompressibility of the vein by probe pressure, absence of spontaneous flow by Doppler ultrasound(29). All diagnostic ultrasonography were performed on patients who reported pain or presented swelling of the catheterized arm. The radiological exams were read by independent radiologists masked to study enrolment and hypotheses.	C. Require therapy
Central line associated blood stream infection (CLABSI) :	Primary BSI in a patient that had a PICC within the 48-hour period before the development of the BSI and is not bloodstream related to an infection at another site. CLABSI diagnosis was made using the definition of the National Health Safety Network (NHSN) (30)by an infection control practitioner and a microbiologist who were masked to the study enrolment and hypothesis.	D. Require major therapy, unplanned increased in level of care, prolonged hospitalization (>48 hours)
Medical adhesive-related skin injury (MARSI):	Redness, tears, or erosion of the skin, or development of vesicles or bulla in an area exposed to medical adhesive and lasting for 30 minutes or more following adhesive removal (31) leading to catheter removal.	B. Nominal therapy, no consequence
Insertion site reaction/infection	Infection or reaction at the insertion site leading to catheter removal.	B. Nominal therapy, no consequence
Leaking	Presence of constant leakage of serous fluid from the insertion site, leading to reinsertion of the catheter.	B. Nominal therapy, no consequence, includes overnight admission for observation only
Migration	Movement of the catheter tip greater than 0.5 cm without loss of function even though the catheter tip may have no longer remained in a central position (28). Migration was diagnosed with a Chest x-ray.	A: No therapy, no consequence or (if catheter was not reinserted) B: B. Nominal therapy, no consequence (if catheter was reinserted)
Occlusion:	Inability to infuse or inject solution into a	B. Nominal therapy,

	catheter; the inability to aspirate blood from a catheter or both(31) resolved with use of a thrombolytic agent or lead to loss of function.	no consequence
Pain	Spontaneous mention by the patient of significant and persistent pain leading to catheter removal or diagnostic imaging.	B. Nominal therapy, no consequence
Suspected Infection	Signs and symptoms of infection (fever, general malaise, elevated WBC), with or without positive blood culture leading to removal of the catheter but not meeting the definition criteria of a CLABSI. Decision to remove the catheter was made by the treating physician who was blinded to the study enrolment and hypothesis.	D. Require major therapy, unplanned increased in level of care, prolonged hospitalization (>48 hours)
Pulmonary embolism	Diagnosed with CT. No documented site of venous thrombosis other than the catheterized vein. Diagnostic made by radiologist blinded to the study enrolment and hypothesis.	D. Require major therapy, unplanned increased in level of care, prolonged hospitalization (>48 hours)

Table 2. Study population		
	Right side insertion	Left side insertion
Number of patients	103	99
Right handed	89 (86%)	90 (90%)
Left handed	11 (10%)	9 (9%)
Data missing	1 (1%)	2 (2%)
Male	53 (51%)	53 (54%)
Female	50 (49%)	46 (46%)
Malignancy	39 (38%)	33 (33%)
No malignancy	64 (62%)	66 (67%)
Single lumen 4 FR	47 (46%)	54 (55%)
Cook Turbo-Flo ™	28 (27%)	19 (19%)
Medcomp Pro-Picc™	19 (18%)	18 (18%)
Double lumen 5 FR	56 (54%)	45 (45%)
Cook Turbo-Flo ™	11 (11%)	12 (12%)
Medcomp Pro-Picc™	45 (44%)	33 (33%)
Average dwell time (days)	37	39
Total catheter days	3829	3828
Reason for insertion		
Antibiotics	47 (46%)	44 (44%)
Chemotherapy	33 (32%)	28 (28%)
Long-term iv access	4 (4%)	5 (5%)
No other access	9 (9%)	3 (3%)
Parenteral nutrition	10 (10%)	19 (19%)

Table 3. Reason for removal		
	Right side n=103 n(%)	Left side n=99 n(%)
Catheter dislodgment	7(7%)	9(9%)
CLABSI	1(1%)	2(2%)
MARSI	1(1%)	1(1%)
CR-Thrombosis	3(3%)	2(2%)
Infection suspected	3(3%)	3(3%)
Insertion site reaction/infection	1(1%)	1(1%)
Leaking	0	1(1%)
Lost follow up	1(1%)	2(2%)
Occlusion	4(4%)	7(7%)
Other type of catheter required	1(1%)	1(1%)
Pain	1(1%)	1(1%)
Therapy completed	80(78%)	69(69%)

Table 4. Complications				
Complications	**Right side n=103 n (%)**	**Left side n=99 n (%)**	**Overall complication % N=202**	**Rate/1000 catheter days**
Catheter dislodgment	8(7.8%)	9 (9%)	8.4%	2.22
Migration	1 (1%)	3 (3%)	2%	0.52
Occlusion	6(5.8%)	11 (11.1%)	8.4%	2.22
CR- UEDVT	4(3.9%)	5 (5%)	4.5%	1.18
Infection suspected	3(2.9%)	3 (3%)	3%	0.78
CLABSI	1 (1%)	3 (3%)	2%	0.52
Insertion site reaction/infection	1(1%)	1 (1%)	1%	0.26
MARSI	2(1.8%)	1 (1%)	1.5%	0.39
Pain	1(1%)	2 (2%)	1.5%	0.39
Leaking	0	1 (1%)	0.5%	0.13
Pulmonary embolism	0	1(1%)	0.5%	0.13

Table 5. Logictic regression result (N=203)				
	OR	CI – 2.5%	CI – 97.5%	p-value (one tailed)
Right sided insertion	**0.581**	**0.306**	**1.087**	**0.046**
Dominant Right arm	1.805	0.610	6.663	0.161
Gender Male	0.852	0.453	1.599	0.308

Presence of malignancy	**2.297**	**1.160**	**4.583**	**0.009**
Size 4 FR Single lumen	0.950	0.492	1.836	0.439
Total Dwell time	1.000	0.993	1.007	0.477
(Intercept)	0.250	0.061	0.836	0.017
p-value overall model : 0.08				