neurocritical care society Neurocrit Care (2016) 25:20–28
DOI 10.1007/s12028-016-0247-9

ORIGINAL ARTICLE

A Randomized Trial of Central Venous Catheter Type and Thrombosis in Critically Ill Neurologic Patients

Jeffrey J. Fletcher[1,2] · Thomas J. Wilson[1] · Venkatakrishna Rajajee[1,3,4] · William R. Stetler Jr.[1] · Teresa L. Jacobs[1,3,4] · Kyle M. Sheehan[1] · Devin L. Brown[3,4]

Published online: 2 February 2016

Abstract

Background Observational studies suggest peripherally inserted central venous catheters (PICCs) are associated with a high risk of catheter-related large vein thrombosis (CRLVT) in critically ill neurologic patients. We evaluated the difference in thrombosis risk between PICCs and centrally inserted central venous catheters (CICVCs).

Methods We conducted a pragmatic, randomized controlled trial of critically ill adult neurologic patients admitted to neurological and trauma critical care units at two level I trauma centers. Patients were randomized to receive either a PICC or CICVC and undergo active surveillance for CRLVT or death within 15 days of catheter placement.

Results In total, 39 subjects received a PICC and 41 received a CICVC between February 2012 and July 2015. The trial was stopped after enrollment of 80 subjects due to feasibility affected by slow enrollment and funding. In the primary intention-to-treat analysis, 17 (43.6 %) subjects that received a PICC compared to 9 (22.0 %) that received a CICVC experienced the composite of CRLVT or death, with a risk difference of 21.6 % (95 % CI 1.57–41.71 %). Adjusted common odds ratio of CRLVT/death was significantly higher among subjects randomized to receive a PICC (adjusted OR 3.08; 95 % CI 1.1–8.65). The higher adjusted odds ratio was driven by risk of CRLVT, which was higher in those randomized to PICC compared to CICVC (adjusted OR 4.66; 95 % CI 1.3–16.76) due to increased large vein thrombosis without a reduction in proximal deep venous thrombosis.

Conclusions Our trial demonstrates that critically ill neurologic patients who require a central venous catheter have significantly lower odds of ultrasound-diagnosed CRLVT with placement of a CICVC as compared to a PICC.

Keywords Central venous catheters · Upper extremity deep venous thrombosis · Vascular access devices · Venous thrombosis

Introduction

Peripherally inserted central venous catheters (PICCs) are being increasingly utilized in hospitalized patients as alternatives to centrally inserted central venous catheters (CICVCs) [1–6]. Frequently cited reasons include a lower rate of mechanical complications during insertion and ease of placement at the bedside by specialized nursing teams [3, 5, 7]. However, cumulative complication rates may not be decreased with PICCs compared to CICVCs, particularly given the reported increased risk of upper extremity thrombosis [3, 8–12]. Notably, this risk seems to be the highest among critically ill patients and may be magnified in critically ill neurologic patients [3, 12].

Previous trials evaluating central venous catheter (CVC)-related thrombosis have been limited by lack of

✉ Jeffrey J. Fletcher
jflet10121@aol.com

1 Department of Neurosurgery, University of Michigan, 1500 East Medical Center Drive, Room 3552 TC, Ann Arbor, MI 48109-5338, USA

2 Department of Neurosurgery, Bronson Methodist Hospital, Kalamazoo, MI, USA

3 Department of Neurology, University of Michigan, Ann Arbor, MI, USA

4 Department of Stroke Program, University of Michigan, Ann Arbor, MI, USA

assigned intervention, differing endpoints (deep venous thrombosis vs all large vein thrombosis), and differing patient populations. Additionally, in the majority of trials, there has been a lack of systematic search for thrombosis. Hence, the incidence of catheter-related thrombosis varies widely in the literature (0–58 %), leading to low confidence in the true point estimate [3, 9–11, 13–25]. Even less is known about the risk difference between PICCs and CICVCs in critically ill patient populations as randomized interventional trials are lacking.

Given that the risk of catheter-related bloodstream infection is similar between catheter types, and the risk of mechanical complications when placing CICVCs has been significantly reduced in the era of point-of-care ultrasound, the risk difference in venous thromboembolism between catheters carries significant importance [26]. As such, the aim of the peripherally inserted versus centrally inserted central venous catheters in neurological intensive care patients (PICNIC) trial was to evaluate the risk difference for thrombosis between catheters in critically ill neurologic patients. Our hypothesis was that patients assigned PICCs would have a higher risk of catheter-related large vein thrombosis (CRLVT) than those assigned to a CICVC.

Materials and Methods

Study Design

PICNIC was designed as a pragmatic, prospective, randomized, open-label, independently adjudicated outcome trial comparing PICCs with CICVCs in critically ill neurologic patients. All patients required CVCs as part of their care in the intensive care unit (ICU). Patients were randomly assigned in a 1:1 ratio to one of two treatment groups: PICC or CICVC. The trial, led by a study group that included academic investigators and a statistician, was funded by the Michigan Institute for Clinical & Health Research grant support (CTSA: UL1RR024986). The trial was monitored by an internal data safety and monitoring board. The site investigators gathered data that were collected and managed using REDCap electronic data capture tools hosted at the University of Michigan [27]. Data were analyzed by the study team who subsequently wrote and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study. The trial was approved by the institutional review boards at the University of Michigan and Bronson Methodist Hospital. All subjects, or their legal representatives, provided written informed consent before randomization.

Patients and Participation Centers

The study was conducted at two level I trauma centers in Michigan with neurological and trauma critical care units staffed by continuous in-house trauma/critical care or neurological critical care physicians. Both hospitals have experienced vascular access nursing teams. The University of Michigan Hospital is a 1000-bed quaternary care academic teaching hospital and Bronson Methodist Hospital is a 425-bed community teaching hospital.

Patients were eligible for inclusion in the study if they were >17 years of age, admitted to the neurological or trauma critical care unit with a primary diagnosis falling under the umbrella of neurological critical care, and in whom a de novo CVC was required as part of ICU care. Patientswho were not expected to survive for 7 days, were prisoners, had a CVC in the upper extremity in the last 30 days, had a known history of upper extremity thrombosis; patients who fell under the vein preservation program (renal insufficiency with elevated creatinine >2.9 mg/dl or who were undergoing hemodialysis); patients who were likely to need prolonged antibiotic therapy after discharge; or any patient the treating physician felt should not be enrolled were excluded from the study. We did not keep a log of patients who were screened for eligibility [28].

Randomization and Concealment

We used a computer random number generator to select random permuted blocks with a block size of 8 and an equal allocation ratio. Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes stored in a central location.

Intervention

At both institutions, catheters were placed in accordance with institution-wide comprehensive prevention programs based on strategies for prevention of catheter-related bloodstream infections endorsed by the Centers for Disease Control and Prevention (CDC) [29]. Catheters were monitored and maintained by the vascular access and ICU nursing teams. Central venous pressure monitoring, if needed, was performed similarly with either catheter.

PICCs were inserted at the bedside by the vascular access nursing team. A 5F or 6F double- or triple-lumen polyurethane power PICC (Bard Access Systems, Salt Lake City, UT) was used. No anti-thrombotic, antibiotic, or antiseptic materials were used in these lines. Real-time ultrasound guidance, standard maneuvers, and a navigator tip locating system were used during placement to choose

the most appropriate venous access (above the elbow, largest vein) and help guide placement.

CICVCs were placed at the bedside by attending intensivists or by residents and advanced practice providers under direct supervision of the attending intensivist. Ultrasound guidance was used in all internal jugular placements and was available but not required during placement of catheters into the subclavian vein. Study subjects randomized to receive CICVCs received either a 7F triple-lumen, second generation (externally coated [chlorhexidine acetate + silver sulfadiazine] and internally coated [chlorhexidine acetate and base]) antiseptic-coated catheter or an 8.5F quad-lumen catheter (Arrowgard Blue Plus; Teleflex, Morrisville, NC).

All general medical care and surgical care was routine and disease specific. No patient underwent therapeutic hypothermia. No concomitant medications or procedures were prohibited; however, hospital policies cautioned against infusion of phenytoin through PICCs. Per ICU policies, patients received thromboembolism chemoprophylaxis with either subcutaneous heparin 3 times per day, or once daily low-molecular weight heparin. Chemoprophylaxis was initiated on admission to the ICU or on postoperative or post-hemorrhage day #1 unless ongoing bleeding was suspected. All patients had chemoprophylaxis ordered during catheter dwell time; however, we did not monitor compliance. Management of upper extremity large vessel thrombosis was left up to the treating physician and documented in the study database.

Outcome Measures

The primary outcome was the composite of CRLVT or death by 15 days following catheter placement. The inclusion of death in the outcome was to minimize any bias due to the possibility of death prior to obtaining at least 1 ultrasound in this critically ill population. CRLVT included any thrombosis adherent to the catheter and involving the deep veins of the neck, upper extremity, or cephalic or basilic veins above the elbow. Partially or completely occluding thrombus was included in our endpoint; however, small adherent thrombus that was not flow-limiting and thought to represent a fibrin sheath was not classified as CRLVT.

Similar to others, we included thrombosis of the basilic and cephalic veins (above the elbow) in our endpoint, because they are large upper extremity veins that, when thrombosis occurs, are frequently symptomatic [13, 14]. Thrombosis of the deep (brachial, axillary, subclavian, and internal jugular) or large proximal veins (cephalic and basilic) of the upper extremity may lead to pulmonary embolus, pain and swelling, post-thrombotic syndrome, compromised future access, or may predispose to more extensive proximal venous thrombosis [9, 13, 14, 30–35]. Additionally, and from a practical standpoint, symptomatic thrombosis can interrupt and complicate care. This is especially true if the catheter is replaced by another CVC or treatment options such as anticoagulation are considered. Similar to catheter-related infections, upper extremity large vessel thrombosis is associated with increases in length of stay, costs, morbidity, and mortality [9, 13].

Ultrasound was utilized for outcome assessment. Assessment of the upper extremity and neck veins was performed for any suspected thrombosis following placement, and a systematic search for thrombosis was performed weekly at ±48 h (or within 24 h of catheter removal) for 2 weeks if the catheter remained in place per study protocol. The need for a CVC was assessed on daily rounds and unnecessary catheters removed. For these reasons, the number of ultrasounds per patient varied. All venous duplex ultrasonography was done portably with a Siemens Sonoline Antares (Siemens Medical Solutions, Inc., Malvern, PA) or Toshiba Xario XG (Toshiba America Medical Systems, Inc., Tustin, CA) machine. All ultrasonography were read by independent board-certified radiologists masked to study enrollment and hypotheses.

Safety and Exploratory Outcomes

Catheter-related bloodstream infections were adjudicated by an infection control reviewer trained in the CDC definition and masked to study enrollment or hypotheses. Serious mechanical complications during catheter placement were documented, as they have been reported during placement of CICVCs; however, the risk is reduced by experienced operators and has markedly decreased in the era of point-of-care ultrasound [24, 36, 37]. We documented possible catheter-related pulmonary embolus (CRLVT and no other etiology of venous thromboembolism) via chest-computed tomography, catheter-related pneumothorax, hemothorax, major arterial injury, or death. We also chose to explore indication for catheter removal and treatment of any CRLVT.

Selection Bias and Confounding

Other than critical illness and malignancy, active surveillance and catheter tip placement outside the superior vena cava have shown consistent independent associations with PICC-related CRLVT [3, 9, 13, 33, 38–40]. We have previously demonstrated in critically ill neurologic patients that PICC placement in a paretic extremity is strongly associated with thrombosis risk. Furthermore, we have also shown an association with PICC-related CRLVT and a prior history of venous thromboembolism, infusion of osmotic therapy through the catheter, and surgery greater

than 1 h during catheter dwell time [12]. A variety of other risk factors have inconsistently been reported to be associated with CRLVT. We documented primary diagnosis, age, sex, race, catheter size, body mass index >30, and congestive heart failure.

Statistical Analysis

This trial was designed to enroll 186 patients over 2 years in order to have 80 % power at a 5 % significance level, to detect a clinically meaningful difference of 15 % in the rate of the primary outcome between catheter groups. Power analysis was performed using 2-sample, 2-sided test for proportions using normal approximation. The trial design included interim analysis after enrollment of 93 patients to assess whether to stop the trial early for efficacy; however, the trial was stopped permanently after enrollment of 80 subjects due to feasibility affected by slow enrollment and funding.

The primary analysis was based on the intention-to-treat principle. Multivariate logistic regression was used to compare the outcomes by treatment group. Secondary analyses included an as-treated analysis for the primary outcome and both an intention-to-treat and as-treated analysis for the secondary outcome so the potential effects of catheter choice on CRLVT could be further investigated. Given the small sample size and based on biological plausibility, we planned a priori to adjust for age (continuous variable by year) and placement of the catheter on the side of a paretic arm (indicator variable 0 = non-paretic arm and 1 = paretic arm) when evaluating the primary outcome. For the secondary outcome of CRLVT, we adjusted only for the placement of the catheter on the side of a paretic arm. We previously identified that placement of a PICC on the side of a paretic arm was the strongest predictor of CRLVT in critically ill neurological patients [12]. All data were complete except for 1 subject who died prior to undergoing ultrasound evaluation and was excluded from the secondary analysis of CRLVT.

The adjusted and unadjusted odds ratios and risk differences are reported with 95 % confidence intervals. For descriptive and bivariate analyses, continuous variables were screened for normality using normality plots and the Shapiro–Wilks test. Parametric data were expressed as means and standard deviations, and non-parametric data were expressed as medians and interquartile ranges. Univariate comparison of continuous variables with a normal distribution was assessed with 2-sample t tests, and continuous variables not meeting the normality assumption were assessed with the Wilcoxon Rank Sum test. All categorical data were tabulated and presented as proportions. Categorical bivariate comparisons were assessed by Chi-square tests or Fisher exact test, as appropriate. Incidence rates of CRLVT were also expressed per 1000 catheter days. All p values are 2-sided, and a p value <0.05 was considered statistically significant. Statistical analysis was performed using commercially available software, SAS 9.4 (SAS Institute, Cary, NC).

Results

Enrollment and Baseline Demographics

A total of 80 subjects were enrolled in the study between February 2012 and July 2015, and all subjects completed the study for evaluation of the primary outcome. At least 1 ultrasound was obtained in 79 subjects with a median time to first ultrasound of 7 days. Forty-one patients received 2 ultrasounds (median day 11), 15 patients received 3 ultrasounds (median day 15), and 2 patients received 4 ultrasounds (median day 18). Characteristics of the cohort and bivariate comparisons can be seen in Tables 1 and 2. The cohort was predominantly Caucasian (91 %) with a mean age of 60 years, represented the intended patient population, and was well-matched except for placement of the catheter on the side of a paretic extremity, which was more common in the CICVC group.

Treatment Assignments, Cross-Overs, and Protocol Details

In total, 39 subjects were assigned to receive a PICC and 41 subjects were assigned to receive a CICVC. After randomization, 2 subjects assigned to the CICVC group and 1 assigned to the PICC group received the unassigned catheter for unclear reasons. No subject had a catheter attempt that was aborted and all PICCs were completed at the bedside. One subject had a PICC immediately replaced in the same position after inadvertent removal. Tables 1 and 2 describe catheter placement details and the adherence to outcome assessment. There was good adherence to ultrasound assessment to search for CRLVT as all but 1 subject received at least 1 ultrasound and 50 % of subjects received 2 or more ultrasounds. All catheter tips were in optimal position, residing in the superior vena cava.

Primary Analysis

In the primary analysis, 17 (43.6 %) subjects receiving PICC compared to 9 (22 %) subjects receiving CICVC experienced the primary outcome with a risk difference of 21.6 % (95 % CI 1.57–41.71 %). The adjusted odds ratio of CRLVT or death was significantly higher among patients randomized to receive a PICC compared to a CICVC (adjusted OR 3.08; 95 % CI 1.1–8.65) (Table 3).

Table 1 Admission diagnosis and catheter characteristics ($N = 80$)

Variable	No. of patients (%)
Admission diagnosis	
Ischemic stroke	7 (8.8)
Subarachnoid hemorrhage	32 (40.0)
Intracerebral hemorrhage	8 (10.0)
Other vascular neurology	1 (1.3)
Traumatic brain injury	11 (13.8)
Neuromuscular disease	4 (5.0)
Seizures/status epilepticus	3 (3.8)
Spine	2 (2.5)
Encephalopathy	1 (1.3)
Sepsis/meningitis	7 (8.8)
Respiratory failure	4 (5.0)
Catheter insertion site	
Right basilic vein	24 (30.0)
Right brachial vein	5 (6.3)
Right cephalic vein	0 (0.0)
Right internal jugular vein	11 (13.8)
Right subclavian vein	7 (8.8)
Left basilic vein	8 (10.0)
Left brachial vein	1 (1.3)
Left cephalic vein	2 (2.5)
Left internal jugular vein	2 (2.5)
Left subclavian vein	20 (25.0)
Catheter size	
Centrally inserted central venous catheters	
7-French #25	25 (31.3)
8.5-French #15	15 (18.8)
Peripherally inserted central venous catheters	
6-French triple-lumen	12 (15.0)
5-French double-lumen	25 (31.3)
5-French triple-lumen	3 (3.8)
Cather tip placement	
Superior vena cava	80 (100.0)

The risk of the primary endpoint was not significantly different between centers (17/51 vs 9/29; $p = 0.83$).

Secondary Analysis

In the as-treated analysis, subjects who received a PICC had higher adjusted odds of the composite endpoint (adjusted OR 3.84; 95 % CI 1.32–11.22). Similarly, the risk of CRLVT was higher in those randomized to the PICC group (adjusted OR 4.66; 95 % CI 1.3–16.76) and was nominally even higher in those who received a PICC (adjusted OR 6.97; 95 % CI 1.7–28.51) (Table 3). Expressed per 1000 catheter days, subjects randomized to PICCs (28 vs 8.1) or treated with PICC (30 vs 6.5) experienced more CRLVT per 1000 catheter days than those in the CICVC group. Catheter dwell time until thrombosis was not different between those randomized to PICCs compared to CICVCs (7.2 days vs 10 days; $p = 0.33$). No difference in CRLVT (12/50 vs 5/29; $p = 0.48$) was observed between centers.

The occurrence of proximal deep venous thrombosis was not decreased in PICC subjects. Six of the 13 (46.2 %) subjects randomized to the PICC group had proximal CRLVT (involving the axillary, subclavian, internal jugular, or brachiocephalic veins) compared (by definition) to all 4 subjects with CRLVT in the CICVC group. Of those with distal thrombosis, 1 was an isolated brachial deep vein thrombosis, while the other 6 were cephalic or basilica large vein thrombosis. Despite this, a greater proportion of subjects had symptomatic CRLVT in the PICC group than the CICVC group; however, this did not reach statistical significance (8/13 [61.5 %] vs 1/4 [25.0 %]; $p = 0.3$), and they were more likely to receive anticoagulation as treatment for the CRLVT (10.3 vs 4.9 %; $p = 0.43$). They were also significantly more likely to have their catheters removed due to thrombosis (17.9 vs 2.4 %; $p = 0.05$) or have inadvertent removal of the catheter (12.8 vs 0.0 %; $p = 0.01$) (Table 3). None of the subjects experienced major mechanical complications or catheter-related bloodstream infections.

The risk of CRLVT by PICC caliber received was 37.5 % (9/24), 33 % (1/3), and 33 % (4/12) for double-lumen 5-French, triple-lumen 5-French, and triple-lumen 6-French catheters, respectively. The risk of proximal deep venous thrombosis by PICC caliber received was 16.7 % (4/24), 0 % (0/3), and 8.3 % (1/12) for double-lumen 5-French, triple-lumen 5-French, and triple-lumen 6-French catheters, respectively.

Discussion

This randomized trial showed that in critically ill neurologic patients who require a CVC, and who do not have a recognized contraindication to any specific catheter type, treatment with a CICVC, compared to a PICC, lowers the risk of CRLVT. For every 4 patients exposed to a CICVC, in place of a PICC, 1 CRLVT can be averted. Selection of a CICVC instead of a PICC may lead to less symptomatic thrombosis, exposure to anticoagulation, and inadvertent catheter removal.

The risk of CRLVT in our cohort was high but consistent with 2 recent prospective trials attempting to evaluate the risk of catheter-related thrombosis among catheter types in critically ill or post-critical care hospitalized patients [14, 16]. A recent study designed to evaluate CRLVT risk between PICCs and CICVCs in critical care patients was re-designed after 6 months as a prospective,

Table 2 Bivariate descriptive analysis

Patient characteristics	Overall ($N = 80$)	PICC ($n = 39$)	CICVC ($n = 41$)	p value
Age, years (±SD)	60 (14)	61 (12)	59 (15)	0.54
Catheter dwell time, days (±SD)	12 (6)	12 (7)	11 (4)	0.52
Female	31 (38.8 %)	15 (38.5 %)	16 (39.0 %)	0.96
Obese (BMI ≥ 30)	31 (38.8 %)	12 (30.8 %)	19 (46.3 %)	0.15
Pro-thrombotic state	4 (5.0 %)	0 (0 %)	4 (9.8 %)	0.12
Coagulopathy	5 (6.3 %)	2 (5.1 %)	3 (7.3 %)	1
Cancer	6 (7.5 %)	2 (5.1 %)	4 (9.8 %)	0.68
Congestive heart failure	8 (10.0 %)	3 (7.7 %)	5 (12.2 %)	0.71
History of venous thromboembolism	5 (6.3 %)	1 (2.6 %)	4 (9.8 %)	0.36
Placed in side of paretic arm	27 (33.8 %)	8 (20.5 %)	19 (46.3 %)	0.02*
Surgery >1 h**	22 (27.5 %)	8 (20.5 %)	14 (34.1 %)	0.17
Mannitol	4 (5.0 %)	1 (2.6 %)	3 (7.3 %)	0.62
Hypertonic saline	17 (21.3 %)	7 (17.9 %)	10 (24.4 %)	0.48
Number of ultrasounds				0.63
0	1 (1.3 %)	1 (2.6 %)	0 (0.0 %)	
1	38 (47.5 %)	21 (53.8 %)	17 (41.5 %)	
2	26 (32.5 %)	10 (25.6 %)	16 (39.0 %)	
3	13 (16.3 %)	6 (15.4 %)	7 (17.1 %)	
4	2 (2.5 %)	1 (2.6 %)	1 (2.4 %)	

BMI body mass index, *CICVC* centrally inserted central venous catheter, *PICC* peripherally inserted central venous catheter, *SD* standard deviation

* Statically significant

** Underwent a surgery >1 h during dwell time of the catheter

single-arm (PICC) observational study based on lack of personal equipoise among enrolling physicians, leading to slow enrollment. Despite the belief that PICCs would be associated with fewer complications than CICVCs, the trial was stopped early after interim analysis due to an unexpectedly high rate of symptomatic (20 %) and asymptomatic (58 %) CRLVT among patients with PICCs [14]. In a separate study in which the authors alternated the use of 7-F CICVCs and 5-F PICCs on a monthly basis in patients just prior to discharge from the ICU, a significantly higher proportion of CRLVT was seen with PICCs (27.2 %) compared to CICVCs (9.6 %) on routine ultrasound [16].

Except for the above-mentioned study, our symptomatic thrombosis risk (11.2 % overall; 20.5 % PICCs vs 2.5 % CICVCs) was higher than in many previous cohorts, including a retrospective analysis of PICC-related large vein thrombosis in critically ill neurologic patients (8.4 %) [12]. In our trial, unlike the outcome of CRLVT, which was objective and independently adjudicated by a radiologist masked to study enrollment, the outcome of "symptomatic" was subjective and determined in unmasked fashion by a study team member. However, based on differences in indications for removal and initiation of anticoagulation to treat detected CRLVT within the PICC group, active surveillance in our trial suggested that symptomatic CRLVT occurs more often than previously reported in retrospective studies. Additionally, pulmonary embolus attributed to PICC-related thrombosis occurred in 15 % of symptomatic CRLVT (1.3 % of the cohort) in one critically ill neurologic patient population [35]. A second study reported a similar risk of pulmonary embolus (1 % with an adjusted mortality of 25 %) in patients receiving a PICC; however, imaging studies to effectively rule out other sources were not completed in many patients [9]. It is also important to note that clinically asymptomatic CRLVT may not truly be asymptomatic, as upper extremity deep venous thrombosis may result in asymptomatic pulmonary embolism in 33 % of cases, symptomatic pulmonary embolus in 9 %, and late-post-thrombotic syndrome in 7–46 % of cases and may complicate future venous access and interrupt and complicate care if catheter replacement or anticoagulation are considered [30–32, 34]. Interestingly, inadvertent line removal occurred in 6 patients in the PICC group, suggesting another possible benefit to CICVCs in brain-injured patients who may be more likely to reach and pull out catheters placed in the arm.

Our trial had several limitations. Most notable, enrollment was much slower than anticipated, raising the possibility of lack of personal equipoise despite stated

Table 3 Primary, secondary, and exploratory outcome analyses

Analysis	No. of patients PICC	No. of patients CICVC	Unadjusted odds ratio risk difference (95 % CI)	Adjusted Odds Ratio (95 % CI)	*p* value
Primary outcome analysis	39	41			
Intention-to-treat (randomized) death/CRLVT	17 (43.6 %)	9 (22.0 %)	2.75 (1.04–7.27) 21.64 (1.57–41.71)	3.08 (1.1–8.65)	
Secondary outcome analysis					
Intention-to-treat (randomized) CRLVT	13/38 (34.2 %)	4/41 (9.8 %)	4.81 (1.41–16.46) 24.45 (6.9–42)	4.66 (1.3–16.76)	
As-treated (received) death/CRLVT	18/40 (45.0 %)	8/40 (20.0 %)	3.27 (1.21–8.84) 25 (5.2–44.8)	3.84 (1.32–11.22)	
As-treated (received) CRLVT	14/39 (35.9 %)	3/40 (7.5 %)	6.91 (1.8–26.54) 28.4 (11.27–45.52)	6.97 (1.7–28.51)	
Exploratory and safety outcomes analysis	39	41			
Indication for removal					0.0001*
End of therapy	25 (64.1 %)	38 (92.7 %)			
Thrombosis	7 (17.9 %)	1 (2.4 %)			
Inadvertent removal	5 (12.8 %)**	0 (0.0 %)			
Other	2 (5.1 %)	2 (4.9 %)			
Procedural complications					
Pulmonary embolism (possibly catheter-related)	1 (2.6 %)	1 (2.4 %)			1
Death	5 (12.8 %)	5 (12.2 %)			1
Inadvertent line removal	6 (15.4 %)	0 (0.0 %)			0.01*
Other (hemothorax, pneumothorax, major arterial puncture, CRBSI, catheter-related death)	0 (0.0 %)				

CICVC centrally inserted central venous catheter, *CRBSI* catheter-related bloodstream infection, CRLVT catheter-related large vein thrombosis, *PICC* peripherally inserted central venous catheter

* Statically significant

** Six patients had inadvertent catheter removal, but the catheter was replaced in 1 patient and was not the indication for end-of-study therapy

collective clinical equipoise at the time of trial design. This was also seen in the only other randomized trial aimed at comparing thrombosis risk between CICVCs and PICCs in critically ill patients, which was subsequently re-designed as a PICC single-arm observational study [14]. Although we demonstrated significant and clinically meaningful differences, slow enrollment led to a smaller sample size, lowering statistical precision, and possibly overestimating treatment effect. If slow enrollment was due to lack of personal equipoise, this may have introduced bias into the study. However, the direction of the bias and extent to which it may impact generalizability is unclear. Admittedly, our trial was not designed to look specifically at the consequences of CRLVT, such as catheter-related pulmonary embolus and symptoms such as pain or swelling, post-thrombotic syndrome, compromised future access, quality of life, functional outcome, or isolated catheter-related mortality. This would require a much larger trial for appropriate power with blinded or independent assessment of these outcomes. However, despite the difference in CRLVT in our trial, being driven by large vein thrombosis in the arm and not proximal deep venous thrombosis, significantly more subjects in the PICC group had documented pain and swelling and received anticoagulation. This supports prior work showing that large vein thrombosis is possibly clinically meaningful. Additionally, PICCs also appeared less useful as they were more often inadvertently or deliberately removed. Lastly, our trial was only performed at 2 centers, which may limit generalizability. However, our patient population represented a typical neurological intensive care patient population and no center differences were seen in the risk of death or CRLVT.

Conclusions

Our trial demonstrates that critically ill neurologic patients who require a CVC have significantly lower odds of CRLVT with placement of a CICVC as compared to a PICC. Additional study seems warranted comparing safety and efficacy of CVCs in critically ill patient populations.

Acknowledgments This research was funded by the Michigan Institute for Clinical & Health Research grant support (CTSA: UL1RR024986).

Compliance with Ethical Standards

Conflict of Interest Dr. Brown received a Clinical and Translational Science Award from the Michigan Institute for Clinical and Health Research (see below). All other authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the involved institutions and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Horattas MC, Trupiano J, Hopkins S, Pasini D, Martino C, Murty A. Changing concepts in long-term central venous access: catheter selection and cost savings. Am J Infect Control. 2001;29:32–40.
2. Walshe LJ, Malak SF, Eagan J, Sepkowitz KA. Complication rates among cancer patients with peripherally inserted central catheters. J Clin Oncol. 2002;20:3276–81.
3. Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. Lancet. 2013;382:311–25.
4. Greene MT, Flanders SA, Woller SC, Bernstein SJ, Chopra V. The association between PICC use and venous thromboembolism in upper and lower extremities. Am J Med. 2015;128:986–93.
5. Gibson C, Connolly BL, Moineddin R, Mahant S, Filipescu D, Amaral JG. Peripherally inserted central catheters: use at a tertiary care pediatric center. J Vasc Interv Radiol. 2013;24:1323–31.
6. O'Brien J, Paquet F, Lindsay R, Valenti D. Insertion of PICCs with minimum number of lumens reduces complications and costs. J Am Coll Radiol. 2013;10:864–8.
7. Meyer BM. Developing an alternative workflow model for peripherally inserted central catheter placement. J Infus Nurs. 2012;35:34–42.
8. Abdullah BJ, Mohammad N, Sangkar JV, et al. Incidence of upper limb venous thrombosis associated with peripherally inserted central catheters (PICC). Br J Radiol. 2005;78:596–600.
9. Lobo BL, Vaidean G, Broyles J, Reaves AB, Shorr RI. Risk of venous thromboembolism in hospitalized patients with peripherally inserted central catheters. J Hosp Med. 2009;4:417–22.
10. Fallouh N, McGuirk HM, Flanders SA, Chopra V. Peripherally inserted central catheter-associated deep vein thrombosis: a narrative review. Am J Med. 2015;128:722–38.
11. Chopra V, Ratz D, Kuhn L, Lopus T, Lee A, Krein S. Peripherally inserted central catheter-related deep vein thrombosis: contemporary patterns and predictors. J Thromb Haemost. 2014;12:847–54.
12. Wilson TJ, Brown DL, Meurer WJ, Stetler WR Jr, Wilkinson DA, Fletcher JJ. Risk factors associated with peripherally inserted central venous catheter-related large vein thrombosis in neurological intensive care patients. Intensive Care Med. 2012;38:272–8.
13. Evans RS, Sharp JH, Linford LH, et al. Risk of symptomatic DVT associated with peripherally inserted central catheters. Chest. 2010;138:803–10.
14. Trerotola SO, Stavropoulos SW, Mondschein JI, et al. Triple-lumen peripherally inserted central catheter in patients in the critical care unit: prospective evaluation. Radiology. 2010;256:312–20.
15. Bernardi E, Pesavento R, Prandoni P. Upper extremity deep venous thrombosis. Semin Thromb Hemost. 2006;32:729–36.
16. Bonizzoli M, Batacchi S, Cianchi G, et al. Peripherally inserted central venous catheters and central venous catheters related thrombosis in post-critical patients. Intensive Care Med. 2011;37:284–9.
17. Chemaly RF, de Parres JB, Rehm SJ, et al. Venous thrombosis associated with peripherally inserted central catheters: a retrospective analysis of the Cleveland Clinic experience. Clin Infect Dis. 2002;34:1179–83.
18. Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. J Vasc Interv Radiol. 2000;11:837–40.
19. Paauw JD, Borders H, Ingalls N, et al. The incidence of PICC line-associated thrombosis with and without the use of prophylactic anticoagulants. JPEN J Parenter Enteral Nutr. 2008;32:443–7.
20. Paz-Fumagalli R, Miller YA, Russell BA, Crain MR, Beres RA, Mewissen MW. Impact of peripherally inserted central catheters on phlebitic complications of peripheral intravenous therapy in spinal cord injury patients. J Spinal Cord Med. 1997;20:341–4.
21. Schmittling ZC, McLafferty RB, Bohannon WT, Ramsey DE, Hodgson KJ. Characterization and probability of upper extremity deep venous thrombosis. Ann Vasc Surg. 2004;18:552–7.
22. Yap YS, Karapetis C, Lerose S, Iyer S, Koczwara B. Reducing the risk of peripherally inserted central catheter line complications in the oncology setting. Eur J Cancer Care (Engl). 2006;15:342–7.
23. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA. 2001;286:700–7.
24. McGee DC, Gould MK. Preventing complications of central venous catheterization. N Engl J Med. 2003;348:1123–33.
25. Timsit JF, Farkas JC, Boyer JM, et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. Chest. 1998;114:207–13.
26. Safdar N, Maki DG. Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients. Chest. 2005;128:489–95.
27. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
28. Elm JJ, Palesch Y, Easton JD, et al. Screen failure data in clinical trials: are screening logs worth it? Clin Trials. 2014;11:467–72.
29. Marschall J, Mermel LA, Classen D, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. Infect Control Hosp Epidemiol. 2008;29(Suppl 1):S22–30.
30. Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med. 1997;157:57–62.
31. Elman EE, Kahn SR. The post-thrombotic syndrome after upper extremity deep venous thrombosis in adults: a systematic review. Thromb Res. 2006;117:609–14.
32. Kahn SR, Ginsberg JS. The post-thrombotic syndrome: current knowledge, controversies, and directions for future research. Blood Rev. 2002;16:155–65.

33. Ong B, Gibbs H, Catchpole I, Hetherington R, Harper J. Peripherally inserted central catheters and upper extremity deep vein thrombosis. Australas Radiol. 2006;50:451–4.
34. Moser KM, Fedullo PF, LitteJohn JK, Crawford R. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. JAMA. 1994;271:223–5.
35. Fletcher JJ, Stetler W, Wilson TJ. The clinical significance of peripherally inserted central venous catheter-related deep vein thrombosis. Neurocrit Care. 2011;15:454–60.
36. Kusminsky RE. Complications of central venous catheterization. J Am Coll Surg. 2007;204:681–96.
37. Taylor RW, Palagiri AV. Central venous catheterization. Crit Care Med. 2007;35:1390–6.
38. Hingorani A, Ascher E, Lorenson E, et al. Upper extremity deep venous thrombosis and its impact on morbidity and mortality rates in a hospital-based population. J Vasc Surg. 1997;26: 853–60.
39. King MM, Rasnake MS, Rodriguez RG, Riley NJ, Stamm JA. Peripherally inserted central venous catheter-associated thrombosis: retrospective analysis of clinical risk factors in adult patients. South Med J. 2006;99:1073–7.
40. Periard D, Monney P, Waeber G, et al. Randomized controlled trial of peripherally inserted central catheters vs. peripheral catheters for middle duration in-hospital intravenous therapy. J Thromb Haemost. 2008;6:1281–8.