Peripherally Inserted Central Catheter Thrombosis—Reverse Tapered versus Nontapered Catheters: A Randomized Controlled Study

Maxim Itkin, MD, Jeffrey I. Mondshein, MD, S. William Stavropoulos, MD, Richard D. Shlansky-Goldberg, MD, Michael C. Soulen, MD, and Scott O. Trerotola, MD

ABSTRACT

Purpose: To compare the thrombosis rate, ease of insertion, bleeding rate, and complications of a nontapered peripherally inserted central catheter (PICC) versus a reverse tapered PICC.

Methods: This was a prospective randomized, controlled trial conducted in single center. All patients 18–90 years old requiring PICC insertion were considered for the study. All patients were followed until PICC removal. Ultrasound examination of the arm was performed at PICC removal or at 28 days. There were 332 patients randomly assigned—164 to the nontapered PICC group and 168 to the reverse tapered PICC group.

Results: The overall thrombosis rate was 71.9%. The thrombosis rate was 70.4% in the nontapered PICC group and 73.4% in the reverse tapered PICC group ($P = .58$). The symptomatic thrombosis rate was 4.3% in the nontapered PICC group and 3.6% in the reverse tapered PICC group ($P = .75$). The complete thrombosis rate was 15.6% in the nontapered PICC group compared with 20.8% in the reverse tapered PICC group ($P = .44$). There was a statistically significantly higher thrombosis rate in patients with cancer (71.9% vs 66.7%, $P = .002$).

Conclusions: This study showed a high incidence of thrombosis of peripheral veins used for PICC insertion. The implication of this thrombosis is significant in light of the morbidity and potential mortality associated with this condition. A difference in thrombosis rate between devices could not be detected in this study.

ABBREVIATIONS

IFU = instructions for use, PICC = peripherally inserted central catheter
potentially reduce bleeding after catheter placement (14). However, because larger diameter PICCs are associated with higher thrombosis rates (13), the taper near the hub also potentially could result in an increased thrombosis rate, especially at the insertion site. Alternative PICC designs have a uniform diameter from the tip toward the hub (ie, “non-tapered”). This prospective, randomized controlled study was designed to compare the thrombosis rate, ease of insertion, bleeding rate, and complications of a reverse tapered PICC and a nontapered PICC.

MATERIALS AND METHODS

This study was approved by the institutional review board and was conducted in compliance with the Health Insurance Portability and Accountability Act. From August 2008 to December 2010, 339 patients were enrolled in a single institution and randomly assigned to receive either a reverse tapered PICC or a nontapered PICC. The CONSORT flow diagram (Fig) shows the randomization and flow of patients throughout the trial. Seven patients did not receive a PICC after enrollment because of randomization errors and other reasons. There were 164 patients who received a nontapered PICC and 168 patients who received a reverse tapered PICC. In 58 patients, the primary endpoint (ultrasound [US] examination) could not be reached. There was no significant difference between the groups in terms of demographics, clinical characteristics, or indications (Tables 1, 2).

Inclusion and Exclusion Criteria

All patients 18–90 years old with a request for a double-lumen PICC indicated for treatment ≥ 2 weeks (our institution’s standard criteria for PICC placement) were considered for the study. Exclusion criteria included the following: (a) coagulopathy (international normalized ratio...
> 2) or thrombocytopenia (platelet count < 25,000/µL); (b) renal insufficiency with creatinine > 3 mg/dL (per our institution’s venous preservation policy based on Kidney Disease Outcomes Quality Initiative guidelines) (15); (c) skin-related problems around the intended insertion site (eg, infection, phlebitis, scars); (d) history of mastectomy or axillary dissection on the insertion side; (e) documented current upper extremity or central venous thrombosis; (f) known hypercoagulable state (eg, protein C or S deficiency, antithrombin III deficiency, lupus anticoagulant); (g) prior enrollment in the trial; (h) therapy needed within 1 hour (emergent placement would not allow sufficient time for proper research consent and randomization); and (i) life expectancy < 1 month.

**Devices**

The PICCs used for the study were 5-F double-lumen reverse tapered PICCs (Bard Access Systems, Salt Lake City, Utah) and 5-F double-lumen nontapered PICCs (Teleflex Medical, Reading, Pennsylvania). The main difference between these two devices is the proximal (ie, hub end) part of the catheter. The reverse tapered PICC diameter increases > 11 cm from 5-F to 7-F at the hub. The nontapered PICC diameter remains uniformly 5-F throughout the length of the catheter.

**Definitions**

Symptomatic thrombosis was defined as the presence of clinical symptoms (pain, arm swelling) and confirmation of venous thrombosis by US. Asymptomatic thrombosis was defined as the presence of clot in the accessed vein (as seen by US) without clinical signs or symptoms.

Partial thrombosis was defined as the presence of clot in the vessel lumen with part of the lumen remaining patent and the presence of Doppler detectable flow. Complete thrombosis was defined as complete obliteration of the vessel lumen by clot. The extent of the thrombus was identified as local (originating in the accessed vein) or extensive (remote from the accessed vein).

**Table 1. Patient Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Nontapered PICC</th>
<th>Reverse Tapered PICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (y) (SD)</td>
<td>53.9 (15.1)</td>
<td>53.9 (14.3)</td>
</tr>
<tr>
<td>Male/female</td>
<td>57.9%/42.1%</td>
<td>54.8%/45.2%</td>
</tr>
<tr>
<td>Brachial vein</td>
<td>58.5%</td>
<td>52.4%</td>
</tr>
<tr>
<td>Basilic vein</td>
<td>40.9%</td>
<td>45.8%</td>
</tr>
<tr>
<td>Cephalic vein</td>
<td>0.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Right arm placement</td>
<td>67.1%</td>
<td>72.0%</td>
</tr>
<tr>
<td>Left arm placement</td>
<td>32.9%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Percent of cancer patients</td>
<td>27.4%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Time to US (d)</td>
<td>21.4</td>
<td>20.7</td>
</tr>
</tbody>
</table>

PICC = peripherally inserted central catheter, SD = standard deviation; US = ultrasound.

**Table 2. Indications for PICC Placement**

<table>
<thead>
<tr>
<th></th>
<th>Nontapered PICC</th>
<th>Reverse Tapered PICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV fluids</td>
<td>40.2%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Infection</td>
<td>39.6%</td>
<td>41.7%</td>
</tr>
<tr>
<td>TPN</td>
<td>26.2%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0.6%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Pressors</td>
<td>5.5%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

IV = intravenous, PICC = peripherally inserted central catheter, TPN = total parenteral nutrition.

**PICC Insertion Procedure**

PICCs were placed using US guidance via the basilic, brachial, or cephalic veins (in decreasing order of preference). Initial evaluation was done by members of the venous access team. The vein diameter was measured with a tourniquet applied, and bedside placement of the PICC was performed. Chest radiography was performed to confirm catheter tip position, ideally at the caval-atrial junction. If bedside placement was unsuccessful, the patient was referred to interventional radiology for imaging-guided placement. Catheters were assessed at day 28, catheter removal, or discharge, whichever came first. At this time, the catheter site was assessed clinically, and US was performed. Catheters were removed when no longer needed or when removal was indicated because of the development of complications.

**US Examination**

US of the ipsilateral arm and central veins was performed to assess for venous thrombosis within 48 hours of catheter removal or at hospital discharge between 14-28 days after PICC insertion, whichever occurred first. If the patient was discharged before 14 days, he or she was asked to return at 28 days. In addition, any patient developing symptoms of venous thrombosis during the study had an US evaluation as clinically indicated. The US examination was performed primarily by the radiology research US laboratory and occasionally by the clinical vascular laboratory or radiology department using a standardized protocol.

Vein imaging was performed using gray-scale US (with and without transverse compression), spectral Doppler,
and color flow Doppler. Two board-certified radiologists interpreted the US scans independently. Both readers were blinded to the type of PICC. In case of any discrepancy, the final interpretation was achieved by consensus.

**Care after the Procedure and Follow-Up**
The PICC was flushed with saline after placement and after each use. The catheter entrance site was inspected daily for signs of infection. Study follow-up ended when the catheter was removed. If the patient was discharged with the PICC, the patient was followed by telephone until PICC removal to record PICC-related adverse events. If the patient experienced a serious adverse event (symptomatic venous thrombosis, severe systemic infection), the patient was followed until resolution of clinical symptoms. Sample size calculation and randomization protocol are presented in Appendix A (available online at www.jvir.org).

**Statistical Analysis**
The two catheter groups were described using means, standard deviations, medians, and interquartile ranges for continuous variables and frequency distributions for categorical variables. To compare groups for continuous and categorical variables, t tests or \( \chi^2 \) tests were used, respectively. Bivariate thrombus risk associations were characterized by odds ratios and 95% confidence intervals. A Mantel-Haenszel stratified \( \chi^2 \) test (16) was used to test the primary hypothesis that the nontapered PICC was superior to the tapered PICC with respect to thrombosis risk (symptomatic or asymptomatic) accounting for the blocked randomization. A Breslow-Day test was used to test whether relative efficacy varied among strata. For the primary efficacy comparison and all further comparisons, a two-sided type I error of \( \alpha = .05 \) was used. For the secondary endpoint of symptomatic thrombosis, bivariate associations were assessed using exact statistical methods because of the small number of cases. Safety endpoints including bleeding rates and insertion complications (overall and for specific complication types) were compared between groups using \( \chi^2 \) and Fisher exact tests.

In addition to testing the a priori specified primary and secondary efficacy hypotheses using the above-described methods, the following post-hoc analyses were performed: (a) comparison of local thrombosis incidence between groups for all patients and in a subset removing cancer patients and (b) comparison of risk results across vessel size categories. Mantel-Haenszel stratified methods were employed to determine catheter group differences and 95% confidence intervals and estimated thrombus rate ratios and odds ratios with confidence intervals as appropriate. A Mantel-Haenszel-Cochran \( \chi^2 \) test was used to test for linear trends in thrombus rates as a function of vessel size category.

Additional analyses were performed to elucidate differences in thrombosis rates between device groups while controlling for vessel size. Vessel sizes were grouped as follows: very small, \(< 2.9\) mm; marginal, \(3–3.9\) mm; small, \(4–4.9\) mm; medium, \(5–5.9\) mm; large, \(> 6\) mm. All analyses were performed using the SAS statistical package (SAS Institute Inc, Cary, North Carolina).

**RESULTS**
The overall thrombosis rate (partial and complete) depicted by US in the cohort was 71.9% (197 of 274 patients). The thrombosis rate was 70.4% (95 of 135 patients) in the nontapered PICC group and 73.4% (102 of 139 patients) in the reverse tapered PICC group (\( P = .58 \) (Table 3)). The symptomatic thrombosis rate was 4.3% (7 of 164 patients) in the nontapered PICC group and 3.6% (6 of 167 patients) in the reverse tapered PICC group (\( P = .75 \) (Table 3)). The complete thrombosis rate was 15.6% (21 of 135 patients) in the nontapered PICC group compared with 20.8% (29 of 139 patients) in the reverse tapered PICC group (\( P = .44 \) (Table 3)). The 7.8% lower local thrombosis rate in the nontapered PICC group compared with the reverse tapered PICC group was not statistically significant (\( P = .19 \) (Table 3)). Overall, patients with cancer had a significantly increased risk of venous thrombosis compared with patients without cancer (71.9% vs 66.7%, \( P = .002 \)).

**Ad Hoc Analysis of the Relationship between Vessel Diameter and Thrombosis**
Vessel size did not differ significantly between groups (Table 4). Table 5 shows the frequency of “local” thrombosis broken down according to vessel diameter. The decreasing thrombosis rate with increasing vessel diameter for nontapered PICCs (100% in “very small” veins to 45.5% in “large” veins) was significant (\( P = .02 \), Mantel-Haenszel \( \chi^2 \) test).

| Table 3. Venous Thrombosis Rates in Nontapered PICC and Reverse Tapered PICC Groups |
|-----------------------------------------------|-------------------------------|-----------------|
| Overall thrombosis rate                      | 95/135 (70.4%)                | 102/139 (73.4%) |
| Symptomatic thrombosis rate                  | 7/164 (4.3%)                  | 6/167 (3.6%)    |
| Asymptomatic thrombosis rate                 | 88/135 (65.2%)                | 96/139 (69.1%)  |
| Complete thrombosis rate                     | 25/164 (15.2%)                | 31/168 (18.5%)  |
| Local thrombosis rate (complete + partial)   | 77/135 (57.0%)                | 90/139 (64.8%)  |

PICC = peripherally inserted central catheter.
Absence (n = 18) of anticoagulation present/bacteremia during the procedure (5.5% [9 of 164 patients] for nontapered PICCs and 2.4% [4 of 168 patients] for reverse tapered PICCs). Similarly, there were no differences between groups in terms of ease of insertion and tip positioning.

Bleeding after the Procedure and Ease of Insertion
There was no statistically significant difference in bleeding rates after the procedure (5.5% [9 of 164 patients] for nontapered PICCs and 2.4% [4 of 168 patients] for reverse tapered PICCs). Similarly, there were no differences between groups in terms of ease of insertion and tip positioning.

Complications
There were 69 complications within this cohort and 14 deaths (unrelated to PICC placement). Of the 69 general complications observed, 28 were in the nontapered PICC group (17% of nontapered PICCs and 40% of all complications), and 41 were in the reverse tapered PICC group (25% of reverse tapered PICCs, or 60% of all complications). Overall, complications did not differ statistically (34.6/1,000 catheter days in nontapered PICCs and 2.4% [4 of 168 patients] for reverse tapered PICCs). Similarly, there were no differences between groups in terms of ease of insertion and tip positioning.

DISCUSSION
One of the most common complications of PICC insertion is venous thrombosis, which can cause significant patient discomfort, can prolong hospitalization, and may require anticoagulation. Often clinically missed, pulmonary embolism from upper extremity sources is 5%-9% (17,18). The reported mortality rate of pulmonary embolism associated with upper extremity deep venous thrombosis is 25% (19).

Postthrombotic syndrome, characterized by chronic swelling of the upper extremity with or without pain, has been reported in 20.8% of patients with upper extremity venous thrombosis at 1 year and 27.3% of patients at 2 years (9). Venous thrombosis associated with a long-term PICC is also important in light of an increase in the number of patients with end-stage renal disease in the United States in recent years (20).

The overall thrombosis rate in this study (71.9%) was the highest among published series to date. A prospective study by Paauw et al (7) showed a 61.9% thrombosis rate on US examination of upper extremity veins in patients with a 5-F PICC. The rate was significantly less (22.9%) in patients who received heparin prophylaxis. In an earlier retrospective study, Allen et al (21) reported a 23.3% PICC-related thrombosis rate demonstrated on venography at the time of subsequent PICC placement. Venography was not performed in patients with symptomatic thrombosis, so this study likely underestimates the overall thrombosis rate. In addition, only 78% of PICCs were 5-F. In another small prospective study, a venous thrombosis rate of 38.5% was demonstrated (22). However, in that study, evaluation for clot was performed using venography with its associated limitations, and 50% of the PICCs were 4-F.

An association between larger PICC diameter and a higher rate of thrombosis has been shown in multiple previous retrospective studies (2,4,13). In a retrospective analysis, Grove and Pevec (13) showed no thrombosis for PICCs < 3-F and 9.8% thrombosis for 6-F PICCs. In another prospective observational study of 2,014 PICCs, Evans et al (2) showed a 0.4% symptomatic thrombosis rate for 4-F PICCs and an 8.8% symptomatic thrombosis rate for 6-F PICCs. Trerotola et al (4) showed the highest symptomatic venous thrombosis rate reported to date (20%) when using 6-F triple-lumen PICCs of a tapered

Table 4. Distribution of Vessel Size (cm) in Nontapered PICC and Reverse Tapered PICC Groups

<table>
<thead>
<tr>
<th>Vessel Size</th>
<th>Nontapered PICC</th>
<th>Reverse Tapered PICC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.29</td>
<td>7 (4.3%)</td>
<td>39 (23.9%)</td>
<td>46</td>
</tr>
<tr>
<td>0.3–0.39</td>
<td>34 (20.9%)</td>
<td>38 (23.3%)</td>
<td>72</td>
</tr>
<tr>
<td>0.4–0.49</td>
<td>39 (23.9%)</td>
<td>45 (27.6%)</td>
<td>84</td>
</tr>
<tr>
<td>0.5–0.59</td>
<td>42 (25.3%)</td>
<td>32 (19.3%)</td>
<td>74</td>
</tr>
<tr>
<td>≥ 0.6</td>
<td>70</td>
<td>48 (28.9%)</td>
<td>118</td>
</tr>
</tbody>
</table>

PICC = peripherally inserted central catheter.

Table 5. Frequency of Local Thrombosis according to Vessel Diameter

<table>
<thead>
<tr>
<th>Vessel Size</th>
<th>Nontapered PICC</th>
<th>Reverse Tapered PICC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.29</td>
<td>100.0% (7/7)</td>
<td>44.4% (4/9)</td>
<td>68.8%</td>
</tr>
<tr>
<td>0.3–0.39</td>
<td>61.5% (16/26)</td>
<td>70.4% (19/27)</td>
<td>66.0%</td>
</tr>
<tr>
<td>0.4–0.49</td>
<td>59.4% (19/32)</td>
<td>66.7% (24/36)</td>
<td>63.2%</td>
</tr>
<tr>
<td>0.5–0.59</td>
<td>55.6% (20/36)</td>
<td>71.4% (20/28)</td>
<td>62.5%</td>
</tr>
<tr>
<td>≥ 0.6</td>
<td>45.5% (15/33)</td>
<td>57.9% (22/38)</td>
<td>52.1%</td>
</tr>
</tbody>
</table>

PICC = peripherally inserted central catheter.
design, and the asymptomatic thrombosis rate as measured by US (using a similar protocol to the present study) was 58%. In a prospective study by Abdullah et al. (22), a venogram was performed before PICC removal. This study showed a 38.5% asymptomatic thrombosis rate with most (85%) being complete thrombosis.

In evaluating risk factors for thrombosis, we identified a statistically significant higher rate in patients with cancer (71.9% cancer vs 66.7% noncancer, \( P = .002 \)). This finding confirmed known higher PICC-associated thrombosis rates in patients with cancer (23–25). For local thrombosis, we identified smaller vessel diameter as a risk factor, at least for nontapered PICCs. Although our study contributes to the growing literature regarding PICC-related thrombosis, our hypothesis that a tapered design would have a higher thrombosis rate than a nontapered design could not be proven.

It is logical to assume that the higher the ratio of the catheter to vein diameter, the higher the rate of thrombosis, and this assumption is supported by the above-described retrospective and nonrandomized studies. A theoretical calculation and modeling of this relationship was performed by Nifong and McDevitt (26). In this model, they showed that there is a statistically significant decrease in flow rates with each successive increase in the catheter diameter. A decrease in flow rates should promote stasis, which, based on Virchow’s theory, causes thrombosis. As noted previously, our study confirmed this relationship in a subset of patients. As to why our hypothesis could not be proven, the most likely explanation relates to a change in design of the reverse tapered PICC and instructions for use (IFU) that occurred shortly after the study began. Recognizing the potential problem of larger diameter of the PICC toward the hub, the updated IFU of the reverse tapered PICC recommend insertion of the PICC only up to the “zero” mark (about 7 cm short of the hub) and not all the way to the hub (27). Although our institution’s experience with tapered devices (4) suggested that in daily practice the reverse tapered PICC would be inserted to the hub and not the “zero” mark, we believed that the study design had to respect the modified IFU. Although our study shows no difference in venous thrombosis rates as labeled for use, further study is needed to determine whether such devices when inserted to the hub might increase the thrombosis rate.

The most important limitation of the present study is in regard to the change in IFU. The sample size and the entire study design were based on published data and theoretical arguments assuming complete insertion to the hub. With the modified IFU (assuming they is followed), it is not a surprise that the rates did not differ because the intravascular portions are similar in diameter when the reverse tapered PICC is used in this way. Because the IFU were followed in nearly all patients with a reverse tapered PICC in this study, the study could not determine what the rate might have been had the device been inserted to the hub. Despite this limitation, because our study is a large, carefully controlled, prospective study, it informs the PICC-related thrombosis literature substantially regardless of the outcome with respect to the taper. Another limitation is that not all of the patients had US performed; this relates to hospital discharge and the difficulty in getting patients back for US scanning. The large number of patients enrolled mitigates this limitation. Finally, we do not know the long-term outcome of the symptomatic and asymptomatic thrombosis observed, and this is an important area of research in the near future.

In conclusion, a high incidence of thrombosis of peripheral veins used for PICC insertion was demonstrated in both arms of this study. In this study, a tapered design did not increase the thrombosis rate, as had been hypothesized. Careful assessment of vessel diameter before placement of a PICC and selection of the smallest diameter PICC able to meet the specific clinical need are of utmost importance. In selected instances, placement of a central line as a substitute for a PICC should be considered.

ACKNOWLEDGMENT

The authors acknowledge the contributions of clinical research coordinators Evelyn E. Stainthorpe, BS, CCRC, Cheryl D. Pugh, AAS, and Jarrod Gutman, BA.

REFERENCES


APPENDIX A: SAMPLE SIZE CALCULATIONS AND RANDOMIZATION DESIGN

Sample Size Calculation
The primary null hypothesis of this study was that the rate of venous thrombosis (asymptomatic or symptomatic) caused by a nontapered PICC is less than the rate of thrombosis caused by a reverse tapered PICC. A priori sample size calculation was based on achieving adequate statistical power to test this hypothesis assuming that the proportions with any thrombosis among nontapered PICC and tapered PICC groups are 0.3 and 0.5. A two-group \(\chi^2\) test with an \(\alpha = .05\) two-sided significance level has at least 85% power to detect the difference between nontapered and tapered catheters, assuming these proportions are 0.3 and 0.5 if the sample sizes in each group are at least equal to 107 (17). To be conservative, the plan was to randomize a population of 135 per group. To determine the final sample sizes, an additional 35 per group were added to 135 to account for missing outcome data.

Randomization
The use of anticoagulation therapy (heparin, warfarin, enoxaparin, and argatroban) and the presence of bacteremia may be highly associated with the incidence of thrombosis in this population. Because of widespread use of anticoagulation and high prevalence of bacteremia in the hospital population studied, it was thought these could not be excluded. To control for these variables, patients were randomly assigned to receive either the nontapered or the tapered PICC within blocks defined on the basis of these variables, as follows:

- Anticoagulation therapy present/bacteremia present
- Anticoagulation therapy present/bacteremia absent
- Anticoagulation therapy absent/bacteremia present
- Anticoagulation therapy absent/bacteremia absent

Randomization within each of the above-listed strata was computer generated in balanced blocks of four such that exactly two were randomly assigned to receive a nontapered PICC and two were randomly assigned to receive a tapered PICC in a random order that varied from block to block. Patients were sequentially evaluated for inclusion and exclusion criteria. Patients meeting all inclusion and exclusion criteria were evaluated for anticoagulation therapy status and bacteremia status. When anticoagulation therapy status and bacteremia status were determined, the next available randomized allocation was obtained from the randomization list for those strata. A randomization code associated with that randomized allocation was recorded into the patient’s record. Randomization codes were used only once, even if some occurrence prevented the patients from receiving a study catheter.