

Subcutaneous tunnelling versus conventional insertion of peripherally inserted central catheters in hospitalized patients (TUNNEL-PICC): A study protocol for a randomized controlled trial

Yohan Kwon

Ajou University Hospital

Eung Tae Kim

Hanyang University Guri Hospital

Soo Buem Cho (✉ sbcho@ewha.ac.kr)

Ewha Womans University <https://orcid.org/0000-0001-5762-7064>

Jae Hwan Lee

Seoul National University Bundang Hospital

Dong Jae Shim

Catholic University of Korea Incheon Songmo Hospital: Catholic University of Korea Incheon Saint Mary's Hospital

Research Article

Keywords: Peripherally inserted central venous catheter, central venous catheterization, central line-associated bloodstream infections, catheter-related bloodstream infections

Posted Date: May 6th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-850405/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Peripherally inserted central catheters (PICCs) are now widely used in modern medicine, and associated complications have also increased. Central line associated bloodstream infection (CLABSI) is the most serious complication because it can cause longer hospital stays and increase costs. Furthermore, it can contribute to dire consequences for critically ill patients. Subcutaneous tunnelling for central venous catheters is an accepted method to reduce the risk of CLABSI. However, it is not generally adopted for PICC placement in most hospitals because its safety and efficacy have not been fully evaluated.

Methods: In this multi-institutional, prospective, non-blinded pragmatic randomized controlled trial, 1694 patients treated at five referral hospitals were assigned to one of two parallel arms (conventional and tunnelled PICC groups) using computer-generated stratified randomization. The conventional group underwent PICC placement by the usual practice. In the tunnelled PICC (tPICC) group, additional subcutaneous tunnelling was applied. Patients will be followed until PICC removal or the end of this study. The primary endpoint was whether subcutaneous tunnelling reduced the rate of CLABSI compared to the conventional method. The secondary endpoints are comparison of technical success rates, complications including exit-site bleeding or infection, and procedure time difference between the groups.

Discussion: Subcutaneous tunnelling is a widely used method to reduce catheter-associated infection. However, it has not been thoroughly applied for PICC. A randomized trial is needed to more objectively assess the effects of subcutaneous tunnel in PICC placement. This TUNNEL-PICC trial will provide evidence for the effectiveness of subcutaneous tunnelling to decrease the risk of CLABSI.

Trial registration: Clinical Research Information Service (CRiS) KCT0005521

Introduction

Background and rationale {6a}

Intravenous catheterization plays a pivotal role in patient care in modern medicine. Over the past decade, the use of peripherally inserted central venous catheters (PICCs) has continuously increased due to their advantages over other central venous catheters. They can centrally infuse vesicant or irritant agents from safe peripheral access. They are also versatile, easy to insert, and carry a relatively low rate of infection [1, 2]. However, PICC-associated bloodstream infections have been reported at rates of 0.6-7.4% and are as frequent as with non-tunnelled central venous catheters [1, 3-8]. Central line-associated bloodstream infection (CLABSI) can lead to prolonged hospitalization, higher costs, and serious consequences in critically ill patients [9]. As a manoeuvre to decrease infection rates, subcutaneous tunnelling has been widely used for central venous catheter placement (i.e., cuffed-tunnelled haemodialysis catheter, Apheresis catheter, or implantable venous port) [10]. Although this is accepted as an effective technique to reduce infection, the tunnelling method has not been frequently used in PICC insertion, with the exception of paediatric central line placement [11]. In 2001, Selby et al. reported on the technical feasibility and safety of PICC insertion with subcutaneous tunnelling [12]. A 2019 retrospective study investigated the effect of subcutaneous tunnelling on CLABSI [13], but no randomized controlled trial has compared the effect of subcutaneous tunnelled PICC (tPICC) versus conventional PICC (cPICC) insertion with a focus on CLABSI. We hypothesized that using the subcutaneous tunnel for PICC insertion would effectively reduce the infection rate, even without tunnel-dedicated devices. This multi-institutional, open-label, parallel-group, pragmatic, randomized

controlled trial study is designed to compare the catheter-related bloodstream infection rates of tPICC and cPICC in hospitalized patients.

Objectives {7}

To evaluate the effect of subcutaneous tunnelling in PICC placement on the rate of CLABSI.

Trial design {8}

This trial will be a prospective, randomized, controlled, investigator-initiated, multi-institutional, open-blind study in five referral hospitals in Republic of Korea. The allocation will be a 1:1 ratio of two parallel groups using computerized randomization.

Methods: Participants, Interventions, And Outcomes

Study setting {9}

This multi-institutional randomized controlled trial will be performed in five referral academic hospitals: (1) Ajou University Hospital, (2) Hanyang University Guri Hospital, (3) Ewha Women's University Seoul Hospital, (4) Seoul National University Bundang Hospital, and (5) Incheon St. Mary's Hospital, Catholic University of Korea.

Eligibility criteria {10}

Eligible patients are ≥ 18 years in an in-patient setting who require PICC insertion. Because diagnosis of CLABSI requires at least 48 hours of dwelling time, patients with pending discharge or transfer to another hospital within two days after catheterization will be excluded. Figure 1 shows the CONSORT flow chart of this study. Both tPICCs and cPICCs will be placed by one interventional radiologist at each institution designated for this study.

Who will take informed consent? {26a}

Informed consent will be obtained by investigators of each institution 1 day before PICC placement. In patients with urgent medical necessity, which will be decided by the referring physician, informed consent will be obtained within at least 6 hours of procedure. Investigators will provide information sheets to participants and will provide a detailed explanation of the study before obtaining informed consent.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

We hypothesize that using the subcutaneous tunnel for PICC insertion will reduce the CLABSI rate compared to conventional methods.

Intervention description {11a}

Participants will be allocated into two groups. The cPICC group will have PICC placement with the traditional method under ultrasonography and fluoroscopic guidance in an angiography suite. The tPICC group will undergo PICC placement in same manner and place with additional subcutaneous tunnelling. Most commercially available PICCs contain no tunnellers or Dacron cuffs. Thus, after vein puncture with the access needle, a Nitinol guidewire will be placed as usual. We will make a tunnel 2–3 cm distal to the initial venepuncture site using an additional 18-gauge needle, and the guidewire will be retrogradely passed through the needle. After resolution of the loop over the venepuncture site, a peel-away sheath will be placed over the wire. The catheter will be trimmed to the distance between the venepuncture site and cavoatrial junction plus the subcutaneous tunnel before being inserted in the usual manner. The initial venepuncture and exit-site wounds will be closed by applying a small amount of *n*-butyl-2-cyanoacrylate (Figure 2).

Criteria for discontinuing or modifying allocated interventions {11b}

Patients who do not want to participate in the trial or accidentally lose the PICC within 48 hours after the procedure will be excluded from the study. There are no criteria for modifying allocated intervention.

Strategies to improve adherence to interventions {11c}

This study includes one-time intervention during procedure and is a pragmatic study. There is no need to improve intervention adherence.

Relevant concomitant care permitted or prohibited during the trial {11d}

Not applicable.

Provisions for post-trial care {30}

Subcutaneous tunnelling is a widely used procedure for central venous catheter placement with no reported serious complications. However, investigators will try to attenuate any damage from the intervention. When it is impossible to recover from irreversible injury, an insurance program for this study will provide compensation. Patients will not be compensated for their participation in the study.

Outcomes {12}

The primary outcome is the effect of subcutaneous tunnelling in PICC placement on the rate of CLABSI. For this, we will use the National Healthcare Safety Network surveillance definition [14]. CLABSI will be defined as a laboratory-confirmed bloodstream infection where the PICC is in place more than 48 hours and must meet both of these criteria: participants have a recognized pathogen identified from one or more blood specimens by a culture- or non-culture-based microbiologic test, and organisms identified in the blood are not related to an infection at another origin (e.g., mucosal-barrier injury). CLABSI will be diagnosed by a board-certified infectionologist at each institution, who is independent to this study for blinding.

The secondary outcomes include rates of local infection and bleeding from exit sites, extra procedure time for subcutaneous tunnelling, and technical success defined as the rate of successful catheter tip placement to the cavoatrial junction. We will divide technical success into two categories. If there is a failure in puncturing the target vein or placing the catheter to the cavoatrial junction, we will define it as 'impossible PICC'. In case of subcutaneous tunnelling failure after target vein puncture, we will define it as 'impossible tunnelling'.

Participant timeline {13}

	STUDY PERIOD			
	Enrolment	Allocation	Post-allocation	Close-out
TIMEPOINT**	-1-3 days	0	<i>Until catheter removal or hospital discharge</i>	<i>After catheter removal or hospital discharge</i>
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Demographic information	X			
Allocation		X		
INTERVENTIONS:				
<i>Conventional PICC</i>			X	
<i>Tunnelled PICC</i>			X	
ASSESSMENTS:				
<i>Demographics</i>	X			
<i>Laboratory test</i>	X			
<i>Procedure details</i>			X	
<i>Procedure-associated complications</i>			X	
<i>Delayed complications</i>				X

Sample size {14}

According to previous reports about PICC, infection rates range from 0.6 to 7.4% [1, 3-5]. In a previous retrospective study, the CLABSI rate of tPICC was 2.6% [13]. Sample size was calculated by assuming the same infection rate in this trial to verify the prior retrospective study result. In this trial, 2 677 participants are needed to prove a reduction of the infection rate from 6.2% to 2.6% for the primary outcome, at a two-sided α level of 0.05 and statistical power of 90%. A total of 1694 participants will be included in this study to account for a 20% of dropout rate (PASS, version 16, NCSS statistical software). Data will be analysed on an intention-to-treat basis according to their originally assigned group.

Recruitment {15}

All hospitalized patients requesting PICC will be potential candidates in this study according to the inclusion and exclusion criteria. When obtaining informed consent, there will be respectful discussions with each candidate to ensure prudent decisions of the patients. A total of 339 patients will be enrolled from each of the five institutes by non-competitive recruitment.

Assignment of interventions: allocation

Sequence generation {16a}

Randomization numbers will be generated by R program (blockrand function in the package “blockrand”) using a 1:2 to 1:6 random block. Multiple datasets were generated by an independent statistician, and an independent research organizer (Medsoft, Hwasung Gyeonggi, Korea) will apply one of the datasets to the electronic Case Report Form (e-CRF) while blinded.

Concealment mechanism {16b}

Just before the procedure and after aseptic skin preparation, a circulating nurse who is not part of this trial will access the secure, password-protected, online-randomized database. The nurse will inform the investigator that the subject is in the cPICC or tPICC group.

Implementation {16c}

The computer-generated block randomization list will be created by an independent statistician. All hospitalized patients who will access PICC and are referred to department of interventional radiology where investigators invited them to participate in this trial. Participants will be sent to the angiography suite and randomly assigned to a group immediately before the procedure by an independent circulating nurse in the angiography suite.

Assignment of interventions: Blinding

Who will be blinded {17a}

There is unavoidable risk of bias in this type of randomized controlled trial where the intervention cannot be blinded to interventionists, participants, or care providers. However, this study has a single-blind characteristics due to following reasons. Participants can only presume their procedure on the grounds of their scar, but they cannot be assured about their group because procedures will be performed under aseptic drapes that screen the patient’s visual confirmation. It is difficult to know whether a tunnel is made or not because they are subcutaneous, and multiple skin incisions can also be made for conventional PICC. Furthermore, the interventionist will not confirm their group. As for care providers, mainly ward nurses can also presume the group but cannot be assured of the allocations for the same reasons as the participants. Outcome assessors will be blinded to allocation. The e-CRF on allocation will not be accessible to outcome assessors. Data analysts will be blinded until the end of study.

Procedure for unblinding if needed {17b}

This study is unblinded.

Data collection and management

Plans for assessment and collection of outcomes {18a}

In line with pragmatic study, the participants will be treated for their own condition according to the initial treatment plan. Daily physical examination and laboratory tests will be performed on a treatment schedule. When the participants have a symptom or sign of infection, blood culture and laboratory testing will be performed as

usual management. Laboratory tests include white blood cell count with differentiation, erythrocyte sedimentation rate, and C-reactive protein level.

Plans to promote participant retention and complete follow-up {18b}

This study plans to enrol hospitalized patients, and adverse events (AEs) will be evaluated during hospitalization. We have no plan to promote retention.

Data management {19}

All data will be secured in independent online server (Medsoft) outside of the hospitals. The investigators will be responsible for all data entry and management. All data will be checked by at least two investigators.

Confidentiality {27}

All collected data will be coded with a code number and this will be the only reference to participants identification during the study period to maintain anonymity. Informed consent forms will be secured in a locked cabinet in a password locked secure place in each hospital. Data will be stored for 3 years after end of this study according to Enforcement Decree of the Bioethics and Safety Act of Korea. All data will be destroyed after that period, but data storage extension will be possible with Institutional Review Board (IRB) permission.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No laboratory evaluation or biological specimen collection is needed in this study.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Independent sample *t*-tests or Mann-Whitney U tests (continuous variables) and Chi-square tests (categorical variables) will be used to compare the two study groups. The infection rate (CLABSI) will be multiplied by 1000 and divided by total catheter-days [15]. Binary logistic regression will be used to predict infection and infection-related death, adjusting for patient-, device-, and provider-level characteristics. Cox proportional hazards regression will be performed used to estimate adjusted hazard ratios and 95% confidence intervals (CIs) for 'time to infection'. Odds ratios with 95% CIs will be estimated for every complication. A *p* value less than 0.05 will be considered significant.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroups will be divided according to their accompanying diseases including diabetes mellitus, malignant tumour (or haematologic malignancy), immune insufficiency (human immunodeficiency virus infection or organ transplantation), end-stage renal disease, or comorbidity of more than one of those conditions.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Data produced following protocol non-adherence will not be included in the study and will be disclosed. An effort will be made to reduce missing data to a minimum. We will handle missing data with multiple imputation (MICE

Package, R ver. 4.0.3, The R Foundation for Statistical Computing, Vienna, Austria).

Plans to give access to the full protocol, participant level-data, and statistical code {31c}

The full protocol will be available at the registry website and is published here.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The five authors (one from each institute) take full responsibility for scientific validity, study quality, study conduction, procedures, patient management after AEs and quality of final study result and reports. All five authors share information through periodic meetings and discuss the study and appropriate management when problems occur.

Composition of the data monitoring committee, its role, and reporting structure {21a}

Data monitoring will be held by each monitoring members in each institute. During monitoring, a data monitoring committee (DMC) will check whether the source document for the subject is appropriate, confirm that the consent acquisition process and storage are appropriate, review the overall trial performance, conduct e-CRF review, review the researcher's binder, collect any AEs from the subject, and follow. The committee is planning to monitor through verification of safety evaluation and data collection.

Any catheter-related AEs will be checked during the follow-up period and will be recorded at e-CRF. In case of more than grade II AEs, it will be reported to the principal investigator (DJ Shim) within 24 hours. Each DMC member will judge whether the AE is associated with the procedure, and any related AE will be immediate reported to the IRB and principal investigator. Each researcher should report any severe AE (\geq grade III) and any other unexpected problems to the IRB within 15 days.

Three independent members will be appointed to the data and safety monitoring board (DSMB; Seungjae Lee [Department of Applied Bioengineering, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea], Young Seo Cho [Department of Radiology, Hanyang University Guri Hospital, Guri-si, Gyeonggi-do, Republic of Korea], Minuk Kim [Department of Radiology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center]).

Adverse event reporting and harms {22}

AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) guideline [16]. If more than three minor AEs ($<$ grade III) occur at one site, the investigator of that site will report the AEs to the DSMB. In case of one severe AE (CTCAE III, IV or V), a DSMB meeting will be held for safety evaluation. Daily checks for each case will be held by the research team of each institution, and will be communicated with the other research teams.

Frequency and plans for auditing trial conduct {23}

Patient monitoring by an independent monitor will take place until each of the new 200 cases are collected or every 3 months if cases do not reach 200. The inspection centre of each institution appointed inspectors to conduct

systematic inspections of trial-related activities and documents. Evaluation of the patients and data will be totally independent from the investigators of each institution and the trial sponsors.

Interim analyses {21b}

Interim analyses will not be performed.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Any change of this trial protocol will be reported to the IRB of each institute and trial registry.

Dissemination plans {31a}

The results of this study will be published in a peer-reviewed medical journal.

Discussion

This TUNNEL-PICC trial will assess the effectiveness of subcutaneous tunnelling on PICC placement pertaining to the CLABSI rate. The results of this study will provide evidence for the application of subcutaneous tunnelling for PICC insertion and be helpful for reducing catheter-associated infection.

PICCs have been widely used in contemporary medical practice for their perceived safety, convenience, cost-effectiveness, and versatility. PICC is generally accepted as safe at insertion and relatively free from serious AEs such as CLABSI during the dwelling period [1]. However, recent reports indicated that the incidence of PICC complications is similar to that for standard central venous catheter [5]. This warrants a study adequately designed to verify the effectiveness of an additional subcutaneous tunnelling method over the conventional non-tunnelling method in reducing catheter-related infection.

Techniques and safety regarding subcutaneous tunnelling on PICC were documented by Selby and colleagues [12], but the infection rate in tPICC was not fully evaluated. Kim et al. recently reported that subcutaneous tunnelling could reduce CLABSI in PICC with no significant increase in procedure time [13]. There was one randomized controlled study regarding tunnelling in patients who had undergone chemotherapy [17]. However, they assessed a relatively small number of participants (n = 129) and limited the study population to cancer patients. Thus, a prospective and randomized controlled study is needed to evaluate the effectiveness of subcutaneous tunnelling in PICC. This trial is the first multicentre randomized controlled research to investigate whether tunnel-PICC insertion reduces catheter-related infection.

There are several limitations of this study. First, although participants and care providers cannot be sure of group allocation, they cannot be blinded. However, the outcome assessor will be blinded. Secondly, this study will be conducted in referral teaching hospitals of various sizes with different characteristics. This can contribute to heterogeneous cohort, but also reflects real-world practice.

This study will be the largest multi-institutional pragmatic randomised controlled trial that can provide guidelines for PICC insertion for patients who are vulnerable to infection.

Trial Status

At the time of manuscript submission, 700 patients have been recruited. Initial recruitment started on 16 November 2020. Recruitment and patient follow-up are still ongoing. The approximate date of recruitment completion is June 2022. This protocol is version 1.4 dated 16 June 2020.

Abbreviations

AE

adverse event

CI

confidence interval

CLABSI

central line-associated bloodstream infection

cPICC

conventional peripherally inserted central catheter

CTCAE

Common Terminology Criteria for Adverse Events

DMC

data monitoring committee

DSMB

data and safety monitoring board

e-CRF

electronic Case Report Form

PICC

peripherally inserted central catheter

SVC

superior vena cava

tPICC

subcutaneous tunnelled peripherally inserted central catheter

Declarations

Acknowledgements

We thank all the DSMB members and the trial committee. We also thank Jaehwi Ahn (Division in Biomedical Art, Department of Fine Art, Incheon Catholic University Graduate School) for providing illustrations.

Authors' contributions {31b}

All five authors will perform the procedure in one of the five institutes and conduct the study protocol. ETK and YK wrote and formulated this study protocol. SBC adjusted and reviewed the protocol. JHL set up the data and manages data analysis. DJS is the principal investigator and conceived the trial. All authors read and approved the final manuscript.

Funding {4}

The study was financially supported by Reyon Pharmaceutical Co. and Genoss Co., Ltd.

Availability of data and materials {29}

Datasets generated and/or analysed in this study will be available from the corresponding author on reasonable request after all identifiable information has been removed.

Ethics approval and consent to participate {24}

The trial was approved by each IRB of the enrolled institutes (Catholic University of Korea IRB approval number: XC20DIDS0096, Hanyang University Guri Hospital IRB approval number: HYGuri 2020-07-005, Ajou University Hospital IRB approval number: AJIRB-MED-INT-20-516, Seoul National University Bundang Hospital IRB approval number: B-2004/608-003, Ewha University Seoul Hospital IRB approval number: SEUMC 2020-07-022-009). Written informed consent will be obtained from the participants. This study will be performed according to the ethical standards of the Declaration of Helsinki.

Consent for publication {32}

No identifiable personal data will be published.

Competing interests {28}

The authors declare that they have no competing interests.

References

1. Chopra V, O'Horo JC, Rogers MA, Maki DG, Safdar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2013;34:908–18.
2. Gunst M, Matsushima K, Vanek S, Gunst R, Shafi S, Frankel H. Peripherally inserted central catheters may lower the incidence of catheter-related blood stream infections in patients in surgical intensive care units. *Surg Infect (Larchmt)*. 2011;12:279–82.
3. 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.
4. Grau D, Clarivet B, Lotthe A, Bommart S, Parer S. Complications with peripherally inserted central catheters (PICCs) used in hospitalized patients and outpatients: a prospective cohort study. *Antimicrob Resist Infect Control*. 2017;6:18.
5. Lee JH, Kim ET, Shim DJ, Kim IJ, Byeon JH, Lee IJ, et al. Prevalence and predictors of peripherally inserted central catheter-associated bloodstream infections in adults: A multicenter cohort study. *PLoS One*. 2019;14:e0213555.
6. Chopra V, Ratz D, Kuhn L, Lopus T, Chenoweth C, Krein S. PICC-associated bloodstream infections: prevalence, patterns, and predictors. *Am J Med*. 2014;127:319–28.
7. Bouzad C, Duron S, Bousquet A, Arnaud FX, Valbousquet L, Weber-Donat G, et al. Peripherally Inserted Central Catheter-Related Infections in a Cohort of Hospitalized Adult Patients. *Cardiovasc Intervent Radiol*.

2016;39:385–93.

8. Herc E, Patel P, Washer LL, Conlon A, Flanders SA, Chopra V. A Model to Predict Central-Line-Associated Bloodstream Infection Among Patients With Peripherally Inserted Central Catheters: The MPC Score. *Infect Control Hosp Epidemiol.* 2017;38:1155–66.
9. Mollee P, Jones M, Stackelroth J, van Kuilenburg R, Joubert W, Faoagali J, et al. Catheter-associated bloodstream infection incidence and risk factors in adults with cancer: a prospective cohort study. *J Hosp Infect.* 2011;78:26–30.
10. Randolph AG, Cook DJ, Gonzales CA, Brun-Buisson C. Tunneling short-term central venous catheters to prevent catheter-related infection: a meta-analysis of randomized, controlled trials. *Crit Care Med.* 1998;26:1452–7.
11. Lawson BT, Zealley IA. Adult 'PICC' Device May be Used as a Tunnelled Central Venous Catheter in Children. *Cardiovasc Intervent Radiol.* 2018;41:645–52.
12. Selby JB Jr, Cohn DJ, Koenig G. Peripherally inserted tunnelled catheters: a new option for venous access. *Minim Invasive Ther Allied Technol.* 2001;10:231–4.
13. Kim IJ, Shim DJ, Lee JH, Kim ET, Byeon JH, Lee HJ, et al. Impact of subcutaneous tunnels on peripherally inserted catheter placement: a multicenter retrospective study. *Eur Radiol.* 2019;29:2716–23.
14. Bloodstream Infection Event In: National healthcare Safety Network (NHSN) Patient Safety Component Manual. (2021). https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf Accessed 2 July 2021.
15. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc.* 2006;81:1159-71.
16. Common Terminology Criteria for Adverse Events (CTCAE). v5. 0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf Accessed 2 July 2021.
17. Xiao MF, Xiao CQ, Li J, Dai C, Fan YY, Cao HJ, et al. Subcutaneous tunneling technique to improve outcomes for patients undergoing chemotherapy with peripherally inserted central catheters: a randomized controlled trial. *J Int Med Res.* 2021;49:3000605211004517.

Figures

Figure 1

The CONSORT flow chart of this study

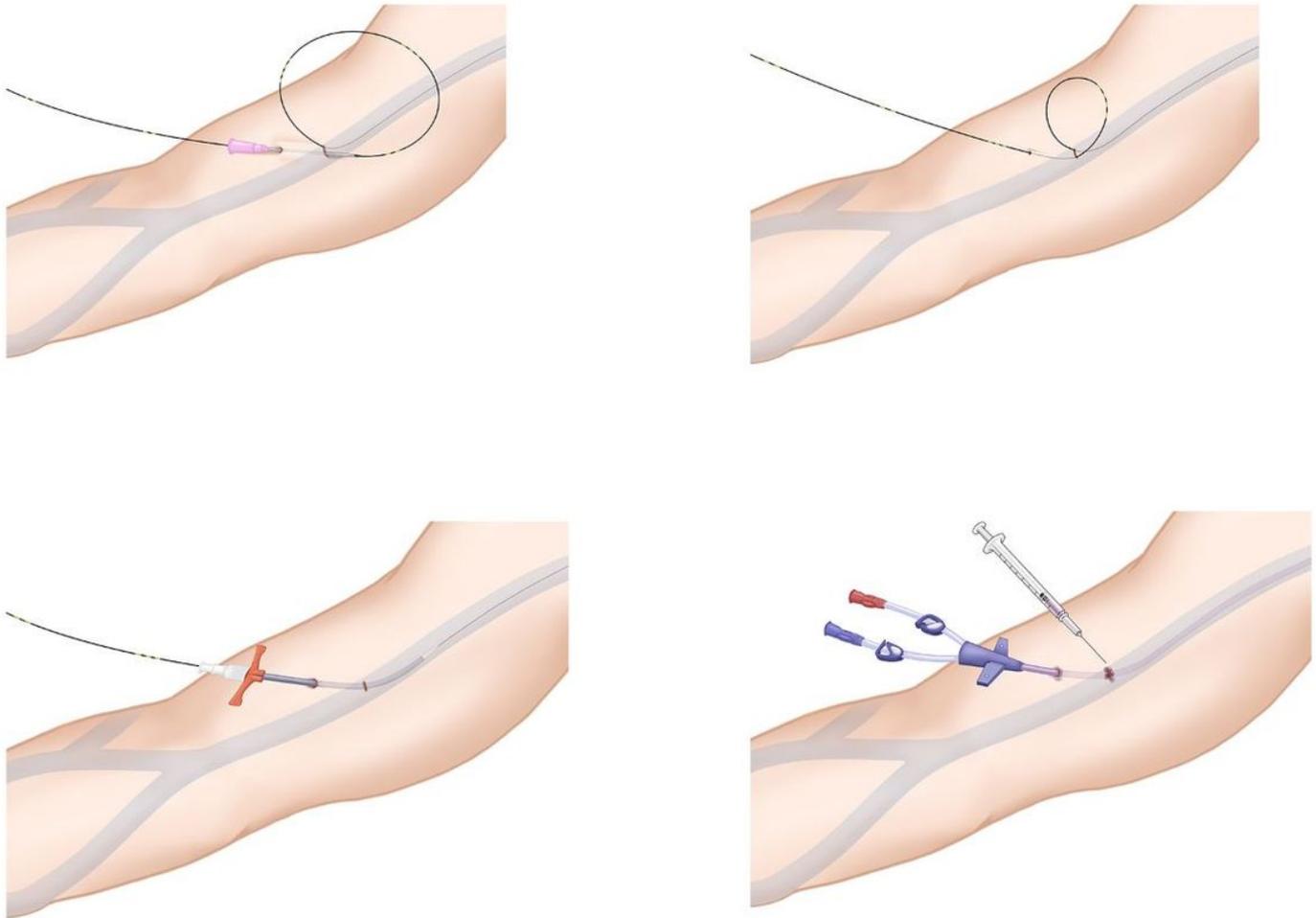


Figure 2

A. Subcutaneous tunnel creation while placing a peripherally inserted central catheter (PICC). First, venepuncture under ultrasonography guidance will be performed with a puncture needle included in the PICC set, and a guidewire will be placed at an upper arm vein. Then, a subcutaneous tunnel will be created with an 18-gauge needle 1-inch away from the initial venepuncture site.

B. A guidewire will be passed through the needle under the subcutaneous tunnel. The loop will be resolved with gentle snapping of the guidewire.

C. A peel-away sheath will be placed in the vein under the subcutaneous tunnel and over the guidewire.

D. Both wounds (initial venepuncture and catheter-exit sites) will be closed with a glue (Histoacryl; B. Braun, Rubí, Spain).