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REVIEW PROTOCOL

Effectiveness of the peripherally inserted central catheter for hematopoietic stem cell transplantation: a systematic review protocol*

Ana Paula Gadanhoto Vieira[1]
ORCID: 0000-0001-7183-7471

Bruno Kosa Lino Duarte[1]
ORCID: 0000-0002-6155-3253

Priscila Silva Urquisa[1]
ORCID: 0000-0003-4046-4136

Maria Helena de Melo Lima[1]
ORCID: 0000-0001-6521-8324

Daniela Fernanda dos Santos Alves[1]
ORCID: 0000-0002-0891-518X

[1]Campinas State University, Campinas, SP, Brazil

Editores:
Ana Carla Dantas Cavalcanti
ORCID: 0000-0003-3531-4694

Paula Vanessa Peclat Flores
ORCID: 0000-0002-9726-5229

Thalita Gomes do Carmo
ORCID: 0000-0002-5868-667X

Corresponding author:
Daniela Fernanda dos Santos Alves
E-mail: dannyfer@unicamp.br

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ABSTRACT

Objective: to assess the effectiveness and safety of the peripherally inserted central catheter for hematopoietic stem cell transplantation. **Methods:** this review will follow the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the search steps will be presented through the flow diagram. The search strategy aims to locate both published and unpublished studies. No time or language restrictions will be applied. The review will consider experimental and observational studies that include adult and pediatric patients undergoing hematopoietic stem cell transplantation. Patients using peripherally inserted central catheters will be compared with those using other central catheters. **Descriptors:** Catheterization, Peripheral; Hematopoietic Stem Cell Transplantation; Systematic Review.

INTRODUCTION

The hematopoietic stem cell transplantation (HSCT) procedure involves the preparation or conditioning phase, hematopoietic stem cell (HSC) infusion, bone marrow aplasia, and hematopoiesis recovery. The preparation or conditioning phase of the patient includes the intravenous administration of chemotherapy, antibiotics, antifungals, analgesics, and antiemetics. Twenty-four hours after the end of conditioning, HSCT is performed by infusing HSCs, stimulating the bone marrow to produce new blood cells and restore the patient's hematopoiesis. The next phase occurs after the transplant and is called bone marrow aplasia; this is considered a critical phase, as it requires specific care and the administration of intravenous medications and blood components until the recovery of the patient's hematopoiesis. The duration of this phase depends on the type of transplant performed and usually takes up to 14 days for patients undergoing autologous transplantation and up to 28 days for those who have received allogeneic transplantation[1].

In all phases of HSCT, the patient must remain with a short or long-term central venous catheter (CVC), which must be effective and safe for intravenous therapy[2]. In Brazil, HSC infusion has been performed through a long-term, semi-implantable, double-lumen, central venous catheter with the largest possible caliber and is implanted using a dissection technique in a surgical center by a vascular medical specialist[3].

Short-term CVC has been replacing semi-implanted long-term central catheters due to the need to manage the surgical schedule and the associated costs and complications, especially primary catheter-related bloodstream infection (CRBSI)[2,4-5]. The CVC (two lumens) is implanted at the bedside by the bone marrow transplantation specialist using a puncture technique. An advanced nurse practitioner or equivalent inserts the peripherally inserted central venous catheter (PICC) in the patient's unit by puncture of a peripheral vein and distal tip of the catheter located in the cavo-atrial junction. For HSCT, experiences in countries like Italy, Spain, and the United States demonstrate that PICC can be used for HSC infusion and all stages of transplantation[6-8]. A recent study demonstrated that the PICC lines were associated with a higher rate of thrombosis and significantly lower CLABSI rates in oncohematologic patients[5]. However, other studies have shown that proper selection of the

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PICC, including consideration of the caliber of the device and the vessel diameter, can reduce the risk of thrombosis[9].

The synergistic effect of thrombotic risk factors supports the importance of risk factor mitigation in every step of the vascular access implantation process. The most predictive measure of thrombosis risk is a previous episode of thrombosis. Thrombosis is a direct risk factor for CRBSI, pulmonary embolism, and the viability of future vein access. Prevention and management of thrombosis are vital to PICC practice[10].

We did not find any systematic review comparing the effectiveness and safety of PICC for patients undergoing HSCT with that of CVC in the short or long term. The systematic review aims to assess whether the PICC is effective and safe for patients with oncohematological diseases undergoing HSCT compared to the short or long-term central venous catheter.

METHOD

Protocol and registrations

This review will follow the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P)[11], and the search steps will be presented through the PRISMA flow diagram[12]. This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), under the number CRD42020206709, on September 28, 2020.

Search strategy

The search will be conducted in nine databases: Medline (PubMed), EMBASE, Cochrane Library, Web of Science, EBSCOhost, ProQuest, EPISTEMONIKOS, Scopus, and Virtual Health Library. The search will include gray literature databases, such as Clinical Trials and Google Scholar. Additionally, a search will be carried out using the references of eligible articles. The search will be updated until the qualitative synthesis is carried out. No time or language restrictions will be applied. The draft of the search strategy that will be used in the electronic databases is presented in Figure 1.

Types of participants, interventions, comparator, and designs

Participants. Adult and pediatric patients undergoing HSCT. Studies in which patients received HSCT for non-oncohematological conditions and those whose PICC had a caliber less than 3 French (Fr) will be excluded.

Intervention. Mono or double lumen PICC, implanted at any stage of HSCT, through peripheral venepuncture in the upper limbs (basilic, brachial or cephalic veins), guided or not by ultrasound, with the distal tip of the catheter located in the third space of the vena cava (cavo-atrial junction), confirmed by radiological examination or by intracavitary electrocardiogram.

Comparator. 1) Mono or double lumen short-term central venous catheter, inserted by puncture, guided/assisted or not by ultrasound, into an internal jugular vein or subclavian vein and distal extremity located in the third space of the superior vena cava confirmed by radiological imaging. 2) Mono or double lumen long-term central venous catheter, with or without cuff, inserted by dissection with the distal tip of the catheter located in the third space of the superior vena cava, confirmed by radiological examination.

Designs. Primary studies, randomized clinical trials, quasi-experimental and observational studies will be included. Review studies, reports, and case series will be excluded. No time or language restrictions will be applied.

Types of outcome measures

Removal of the catheter by the completion of therapy: number of patients with the catheter removed at the end of the hematopoiesis recovery phase.

Catheter duration: the number of days the patient stayed with the catheter.

Overall mortality: death from any cause.

Mortality associated with catheter-related complications: death confirmed by complications related to the catheter.

Primary catheter-related bloodstream infection (CRBSI): confirmed by two or more positive paired blood cultures in blood collections from the catheter and peripheral venous access with the same microorganism.

Removal of the catheter due to complications: catheter removed by death, CRBSI, infection at the insertion site, clinical suspicion of infection such as fever of undetermined origin, sepsis, thrombosis, or pain at the insertion site or catheter tunnel (inflammatory signs without improvement).

Catheter-related deep venous thrombosis (DVT): diagnosis of thrombosis related to the catheter,

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Date	Databa-se	Search strategy	Filters or limits	Hits
10 Sept 2020	Medline (PubMed)	((((((((((Bone Marrow Transplantation[MeSH Terms]) OR ("Bone Marrow Transplantation"[Title/Abstract] OR "Grafting, Bone Marrow"[Title/Abstract] OR "Bone Marrow Grafting"[Title/Abstract] OR "Transplantation, Bone Marrow"[Title/Abstract] OR "Bone Marrow Cell Transplantation"[Title/Abstract] OR "Transplantation, Bone Marrow Cell"[Title/Abstract])) OR ((Stem Cell Transplantation[MeSH Terms]) OR ("Stem Cell Transplantation"[Title/Abstract] OR "Stem Cell Transplantations"[Title/Abstract] OR "Transplantations, Stem Cell"[Title/Abstract] OR "Transplantation, Stem Cell"[Title/Abstract]))) OR ((Hematopoietic Stem Cell Transplantation[MeSH Terms]) OR ("Hematopoietic Stem Cell Transplantation"[Title/Abstract] OR "Stem Cell Transplantation, Hematopoietic"[Title/Abstract] OR "Transplantation, Hematopoietic Stem Cell"[Title/Abstract]))) OR ((Transplantation, Autologous[MeSH Terms]) OR ("Transplantation, Autologous"[Title/Abstract] OR Autotransplantation[Title/Abstract] OR Autotransplantations[Title/Abstract] OR Autografting[Title/Abstract] OR Autograftings[Title/Abstract] OR "Autologous Transplantation"[Title/Abstract] OR "Autologous Transplantations"[Title/Abstract] OR "Transplantations, Autologous"[Title/Abstract]))) OR ((Transplantation, Homologous[MeSH Terms]) OR ("Transplantation, Homologous"[Title/Abstract] OR "Allogeneic Transplantation"[Title/Abstract] OR "Transplantation, Allogeneic"[Title/Abstract] OR Homografting[Title/Abstract] OR "Homologous Transplantation"[Title/Abstract] OR "Allogeneic Grafting"[Title/Abstract] OR "Grafting, Allogeneic"[Title/Abstract] OR Allografting[Title/Abstract]))) OR (allotransplantation)) OR (((Peripheral Blood Stem Cell Transplantation[MeSH Terms]) OR ("Peripheral Blood Stem Cell Transplantation"[Title/Abstract] OR "Peripheral Stem Cell Transplantation"[Title/Abstract] OR "Stem Cell Transplantation, Peripheral"[Title/Abstract] OR "Transplantation, Peripheral Stem Cell"[Title/Abstract])) OR ("Peripheral Blood Stem Cell Transplantation (PBSCT)"))) OR ("Peripheral Blood Stem Cell Transplantation (PBSCT)")) AND ((((Catheterization, Peripheral[MeSH Terms]) OR ("Catheterization, Peripheral"[Title/Abstract] OR "Peripheral Catheterization"[Title/Abstract] OR "Catheterizations, Peripheral"[Title/Abstract] OR "Peripheral Catheterizations"[Title/Abstract] OR "Peripherally Inserted Central Catheter Line Insertion"[Title/Abstract] OR "PICC Placement"[Title/Abstract] OR "PICC Placements"[Title/Abstract] OR "Placement, PICC"[Title/Abstract] OR "Placements, PICC"[Title/Abstract] OR "PICC Line Placement"[Title/Abstract] OR "PICC Line Placements"[Title/Abstract] OR "Placement, PICC Line"[Title/Abstract] OR "Placements, PICC Line"[Title/Abstract] OR "PICC Line Catheterization"[Title/Abstract] OR "Catheterization, PICC Line"[Title/Abstract] OR "Catheterizations, PICC Line"[Title/Abstract] OR "PICC Line Catheterizations"[Title/Abstract] OR "Peripheral Venous Catheterization"[Title/Abstract] OR "Catheterizations, Peripheral Venous"[Title/Abstract] OR "Peripheral Venous Catheterizations"[Title/Abstract] OR "Venous Catheterizations, Peripheral"[Title/Abstract] OR "Venous Catheterization, Peripheral"[Title/Abstract] OR "Catheterization, Peripheral Venous"[Title/Abstract])) OR ("Peripherally Inserted Central Venous Catheters (PICCs)" OR "Peripherally inserted central venous catheters")) OR ("peripherally inserted central venous catheter" OR "Lifecath PICC Expert" OR "peripherally inserted central catheter" OR "peripherally-inserted central venous catheter" OR "pic line" OR "picc line" OR "PowerPICC SOLO catheter" OR "Spectrum Turboject"))) AND (((Catheterization, Central Venous[MeSH Terms]) OR ("Catheterization, Central Venous"[Title/Abstract] OR "Venous Catheterization, Central"[Title/Abstract] OR "Central Catheterization"[Title/Abstract] OR "Catheterization, Central"[Title/Abstract] OR "Catheterizations, Central"[Title/Abstract] OR "Central Catheterizations"[Title/Abstract] OR "Central Venous Catheterization"[Title/Abstract] OR "Catheterizations, Central Venous"[Title/Abstract] OR "Central Venous Catheterizations" [Title/Abstract] OR "Venous Catheterizations, Central" [Title/Abstract])) OR ((Central Venous Catheters [MeSH Terms]) OR ("Central Venous Catheters" [Title/Abstract] OR "Catheter, Central Venous" [Title/Abstract] OR "Catheters, Central Venous" [Title/Abstract] OR "Venous Catheter, Central" [Title/Abstract] OR "Venous Catheters, Central" [Title/Abstract] OR "Central Venous Catheter" [Title/Abstract]))))	None	17

Figure 1 - Search strategy. Campinas, SP, Brazil, 2020

Source: Elaborated by the authors, 2020.

confirmed by ultrasonography, venography, echocardiography, or magnetic resonance.
Catheter-related complications: occlusion, rupture, transient or permanent malfunction, externalization, or accidental catheter loss.
Complications associated with catheter insertion: clinical or mechanical complications resulting from the catheter insertion process, such as hematoma at the puncture site, pneumothorax, haemothorax, or death.
Complications at the catheter insertion site: phlogistic signs at the insertion site or in the catheter tunnel and enlargement of the insertion ostium.

Selection of studies, inclusion, and exclusion criteria

The studies identified in the databases will be exported to the Covidence platform, and duplicates will be excluded. On this platform, four researchers (APGV, BKLD, PSU) will screen the titles and abstracts using the eligibility criteria in pairs. Disagreements will be resolved by consensus or consultation with the third reviewer (DFSA or MHML).
The selected studies will be recovered in full, and three researchers (APGV, BKLD, PSU), in pairs, will confirm the study's eligibility by evaluating the full texts and justifications for exclusion. Disagreements will also be resolved through consensus and, when necessary, through consultation with a third researcher (DFSA or MHML).

Quality and bias assessment

For randomized clinical trials, we will use the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), which contains five evaluation domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. Domains are adopted using a guide for the judgments divided into the following options - yes, probably yes, probably not, no, and no information. The studies will be classified based on previous judgments, low risk of bias, some concerns, and high risk of bias[13].
We will use the Joanna Briggs Institute critical evaluation checklist for quasi-experimental and observational studies (cross-sectional, case-control, and cohort studies)[14-15].

Synthesis

The data of similar studies will be summarized through meta-analysis obtained in fixed-effects models. For dichotomous data (removal of the catheter by the completion of therapy, global mortality, mortality associated with catheter-related complications, CRBSI, removal of the catheter due to complications, catheter-related DVT, catheter-related complications, complications associated with catheter insertion, and catheter insertion site), the risk ratios (RR) will be presented using 95% confidence intervals (CI). For continuous data (catheter duration), the results will be treated using mean differences and 95% CI.
Detailed evaluations of the studies will be performed and statistical techniques will be applied to identify heterogeneity and verify if there is a difference in the findings from the studies included in the review. The heterogeneity will be evaluated using the chi-squared test, adopting a significance level of $p < 0.10$ and estimating the inconsistency between studies (I^2). The following limits will assess the magnitude of heterogeneity (I^2): below 40% - not important, 30% to 60% - moderate, 50% to 90% - substantial, and 75% to 100% - considerably heterogeneous. In case of substantial heterogeneity, intervention effect estimates will be calculated using random-effect models. For this analysis, we will use RevMan 5.4 or later. A funnel plot will be generated to assess publication bias if 10 or more studies are included in a meta-analysis. The statistical test for funnel plot asymmetry (Egger test) will be performed where appropriate[16].
If we find enough data for the analysis, we plan to perform subgroup analyses according to age (0 to 18 years, 19 to 60 years, and 61 years or more) and the time of insertion (before and during HSCT). If statistical pooling is impossible, the findings will be presented in narrative form, including tables and figures.
The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) instrument for grading the certainty of evidence will be used[16], and a Summary of Findings (SoF) will be created using GRADEPro GDT (McMaster University, ON, Canada). The outcomes reported in the SoF will be the removal of the catheter by the completion of therapy, global mortality, mortality associated with catheter-related complications, CRBSI, removal of the catheter due to complications, catheter-related DVT, catheter-related complications, complications

associated with catheter insertion, and catheter insertion site[16].

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CONFLICT OF INTERESTS

The authors have declared that there is no conflict of interests.

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AUTHORSHIP CONTRIBUTIONS
Project design: Vieira APG, Duarte BKL, Urquisa PS, Lima MHM, Alves DFS
Data collection: Vieira APG
Data analysis and interpretation:
Writing and/or critical review of the intellectual content: Vieira APG, Duarte BKL, Urquisa PS, Lima MHM, Alves DFS
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