Clinical Research

Central line-associated bloodstream infection related with umbilical vein catheterization and peripherally inserted central catheter in preterm infants: a meta-analysis and systematic review

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ABSTRACT

BACKGROUND Central line-associated bloodstream infection (CLABSI) is a serious complication in preterm infants undergoing catheterization, including umbilical vein catheterization (UVC) and peripherally inserted central catheter (PICC) placement. This study aimed to compare the occurrence rate of CLABSI in preterm infants associated with UVC and PICC.

METHODS We conducted a systematic review and meta-analysis of studies published from 2000 to 2023 using a random effects model from 3 databases (PubMed, ScienceDirect, and Google Scholar). This study was registered with PROSPERO (CRD42023416471).

RESULTS Of 10 articles included in the systematic review, 2 were randomized controlled trials, 3 were prospective studies, and the rest were retrospective. A total of 3,962 UVCs and 2,922 PICCs were incorporated in the meta-analysis. The incidence rate of CLABSI in the UVC group was lower than that in the PICC group (1.23 *versus* 3.03 per 1,000 catheter days). However, the odds of developing CLABSI for infants with a UVC compared to those with a PICC were not statistically significant (odds ratio: 0.88, 95% confidence interval: 0.54–1.42).

CONCLUSIONS UVCs had a lower incidence rate of CLABSI than PICCs. Therefore, additional prospective studies are required to confirm these results.

KEYWORDS bloodstream infection, peripherally inserted central catheter, umbilical veins

Central line-associated bloodstream infection (CLABSI) is a serious complication in preterm infants undergoing catheterization, including umbilical vein catheterization (UVC) and peripherally inserted central catheter (PICC) placement. Despite its benefits, UVC is associated with undesirable events such as thrombosis, infections, and liver dysfunction, which can further complicate the vulnerable health of preterm infants.[1–3] A study showed that the incidence of CLABSI ranged from 2.6 to 8.4 per 1,000 catheter days,[4] while other studies revealed a 60% incidence reduction from 0 to 14.9 per 1,000 catheter days after implementing care bundles.[5]

UVC and PICC are catheterization methods commonly used in neonatal intensive care units (NICUs) to deliver parenteral nutrition and medications to preterm infants. However, they are associated with adverse events such as CLABSI, which can further complicate the preexisting vulnerability of preterm infants to health complications.[6] Among all the

healthcare-associated infections, CLABSIs are also associated with an inflated financial burden.[7]

Although several studies have investigated the incidence and types of undesirable events related to UVC in preterm infants, the results have been inconsistent. Therefore, this study aimed to compare the occurrence rates of CLABSI associated with UVC and PICC and provide clinical practice guidelines for catheterization in preterm infants, thereby improving patient outcomes and reducing resource constraints on healthcare burdens.

METHODS

This study used conventional techniques for systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[8] The research protocol was recorded in the PROSPERO database for systematic reviews (CRD42023416471).

Eligibility criteria

All published randomized controlled trials (RCTs) and observational studies that discussed measures of CLABSI with UVC or PICC and were published between January 2000 and March 2023 were included. We conducted a literature search from May to June 2023. Studies delineated as abstracts were also eligible for inclusion if the data could be obtained or if incomplete data were retrieved after the author was reached. Case reports, review articles, short communications, and letters were excluded.

Outcomes

The primary outcomes were UVC- and PICC-related infections, characterized as unintended events indirectly linked to the device itself, potentially leading to increased illness severity, prolonged hospitalization, or even mortality. CLABSI was interpreted as follows: (1) a primary bloodstream infection (BSI) in a patient who had a central line inserted within 48 hours before the development of the BSI, and the infection was not associated with any other site of infection; and (2) central line-related septicemia, defined as clinical symptoms and laboratory findings along with multiple positive blood cultures for confirmed pathogens or multiple positive cultures for microorganisms while the device was in place.[9,10]

Search strategy

We conducted article searches from three electronic databases (PubMed, ScienceDirect, and Google Scholar), using the keywords "preterm infant" AND "umbilical vein catheterization" OR "peripherally inserted central catheter" with all possible synonyms. In addition, we conducted searches for relevant studies by checking references and citations. To ensure comprehensive coverage and achieve optimal outcomes in the systematic review, we followed the recommendations of Bramer et al.[11] Only the articles published in English between January 2000 and March 2023 were included. Documents from unreviewed and unpublished studies were excluded from the analysis. The corresponding authors were contacted via email, when necessary, to confirm the information in the manuscript.

Selection of the studies

Studies were imported into Zotero (Corporation for Digital Scholarship, USA) and the Rayyan applications (Rayyan System Inc., USA) for duplicate removal and screening purposes.[12] The screening phase was conducted initially by IS and HL and confirmed by BM or HH under the established inclusion criteria. Another reviewer (PPK) resolved this disagreement until a consensus was reached.

Data collection and extraction

Data were gathered using a specific form and entered into Microsoft Excel (Microsoft Corporation, USA) by two authors (IS and HL). Conflicting viewpoints were settled through discussions with a third author (BM). The following data were obtained: name of the first author, country of publication, publication year, title, study design (randomized trial, prospective, or retrospective), population/participant, intervention, comparison, outcome, sample size, gestational age, birth weight, and catheter dwelling time.

Statistical analysis

Descriptive statistics were used to summarize the study population and outcomes. Statistical analyses were performed using MedCalc Statistical Software version 19.6 (MedCalc Software Ltd., Belgium), Comprehensive Meta-Analysis version 3.3 (Biostat, USA), and MetaXL version 5.3 (EpiGear International Pty Ltd., Australia). CLABSI occurrence rates were calculated and reported as a proportion (%) or incidence

rate per 1,000 catheter days, with a 95% confidence interval (CI). A meta-analysis was conducted to analyze both frequency and proportional data, utilizing Freeman–Tukey double arcsine transformations to stabilize the variance in proportions and incidence rates across studies. Pooled estimates for the incidence ratio using the generic inverse variance method were calculated.[13,14]

Each effect measure of the included studies was summarized as a pooled effect measure in a forest plot. Odds ratios (ORs) not presented in the articles were calculated based on the available data. The combined OR indicates the intensity of the relationship between the incidence of CLABSI and the intervention performed (UVCs or PICCs). Owing to substantial variation across studies, combined estimates were determined using random effects models.[15]

Heterogeneity was evaluated using Cochran's Q and I^2 metrics. A study was considered to exhibit heterogeneity if the *p*-value for Cochran's Q test was <0.1. Heterogeneity was categorized into four levels: 0–25% (low), 25–50% (low to moderate), 50–75% (moderate to high), and ≥75% (high).[16] We employed funnel and Doi plots to identify possible publication bias. Publication bias was revealed either by Egger's test results of $p<0.05$ in the funnel plot or by the asymmetric Doi plot according to the Luis Furuya-Kanamori (LFK) index.[17]

Quality of eligible studies

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[18] determined bias in observational studies, whereas the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist[19] assessed bias in RCTs. Each element in the STROBE and CONSORT checklists was assigned one point. Studies that received a cumulative score of 1–7 were categorized as having a high risk of bias, 8–14 as moderate risk, and 15–22 as low risk. For the CONSORT checklist, scores of 1–8 were categorized as high risk of bias, 9–16 as moderate risk, and 17–25 as low risk.

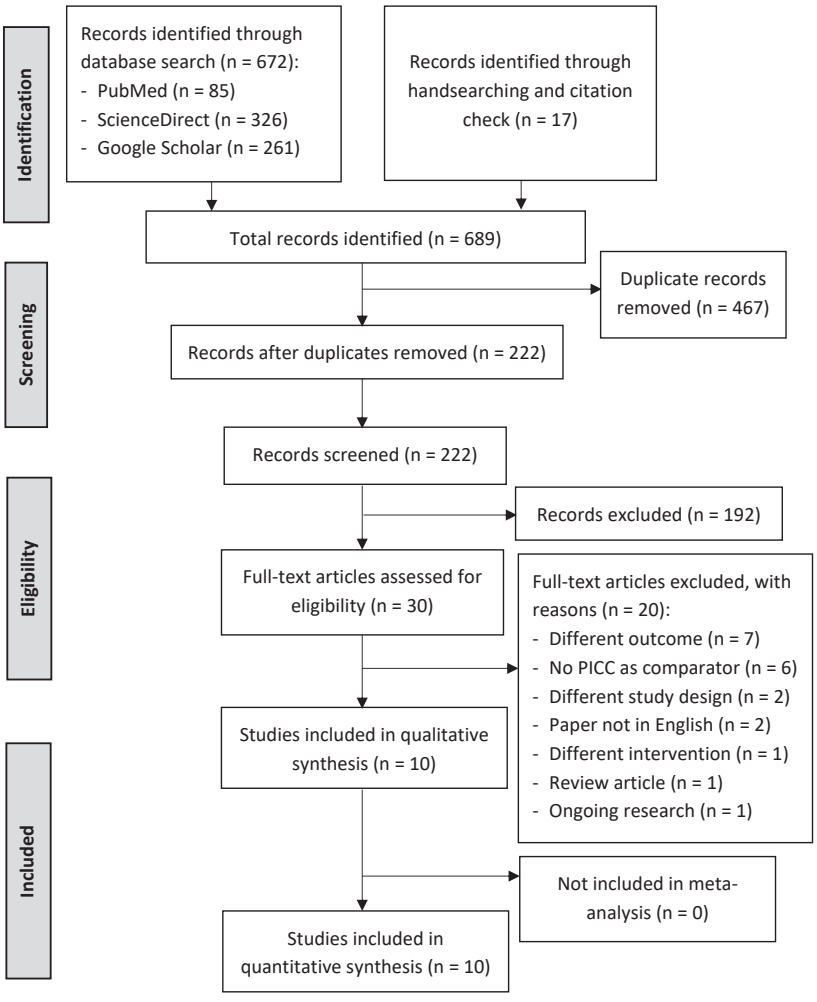

Figure 1. Study selection flowchart.
PICC=peripherally inserted central catheter

Table 1. Summary of each study

First author, year	Place	Study design	Study size, n	Occurrence of CLABSI, n (incidence/1,000 catheter days)		Birth weight (g), mean (SD)	Gestational age (weeks), mean (SD)	Catheter indwelling time (days), mean (SD)	
				UVC	PICC			UVC	PICC
Butler-O'Hara,[20] 2006	USA	RCT	210	104 (11.5/1,000)	106 (7.4/1,000)	922.92 (195.23)	27.75 (2.14)	11.5 (5–25)*	14 (5–28)*
Dongara,[21] 2017	India	RCT	144	72 (14.2/1,000)	72 (6.5/1,000)	2,111 (768)	34.75 (4.14)	4.88 (3.23)	8.57 (5.38)
Konstantinidi,[22] 2019	Greece	Prospective cohort	71	37 (2.6/1,000)	34 (2.3/1,000)	1,037 (196.5)	28.6 (2.15)	10.43 (5.38)	11.91 (6.93)
Hei,[23] 2012	China	Prospective cohort	516	285 (14.2/1,000)	231† (9.8/1,000)	2,395.19 (928.08)	33.67 (5.75)	6.69*	7*
Zingg,[24] 2011	Switzerland	Prospective cohort	1,124	1,393 (19/1,000)	723 (80/1,000)	1,943 (1,012)	32 (29–37)*	4.3 (2.5)	7.8 (4.7)
Arnts,[25] 2014	Netherlands	Retrospective cohort	203	140 (21/1,000)	63 (12/1,000)	1,758 (1,027.5)	31.9 (4.7)	6.9 (2.7)	10.2 (5.2)
Shalabi,[26] 2015	Canada	Retrospective cohort	540	180 (7.8/1,000)	180 (9.3/1,000)	1,021 (246.68)	27.20 (1.49)	8 (6–10)*	13 (9–19)*
Yumani,[27] 2013	Netherlands	Retrospective cohort	196	180 (22.1/1,000)	49 (14.4/1,000)	1,475 (1,100–2,661)*	32 (29–36)*	7 (4–9)*	9 (5–15)*
Sanderson,[28] 2017	Australia	Retrospective cohort	3,985	1,392 (3.3/1,000)	1,317 (4.8/1000)	2,201 (1,470.33)	34.08 (7.18)	4 (2–6)*	8 (5–11)*
Nielsen,[29] 2022	Denmark	Retrospective cohort	382	179 (12/1,000)	147 (25/1,000)	1,562 (1,047.32)	30.65 (5.26)	4 (2–6)*	8 (5–12)*

CLABSI=central line-associated bloodstream infection; PICC=peripherally inserted central catheter; RCT=randomized controlled trial; SD=standard deviation; UVC=umbilical vein catheterization

*Data are presented in median (interquartile range [IQR]); †although the control group had peripheral venous access, they were still included in the meta-analysis (as imputation)

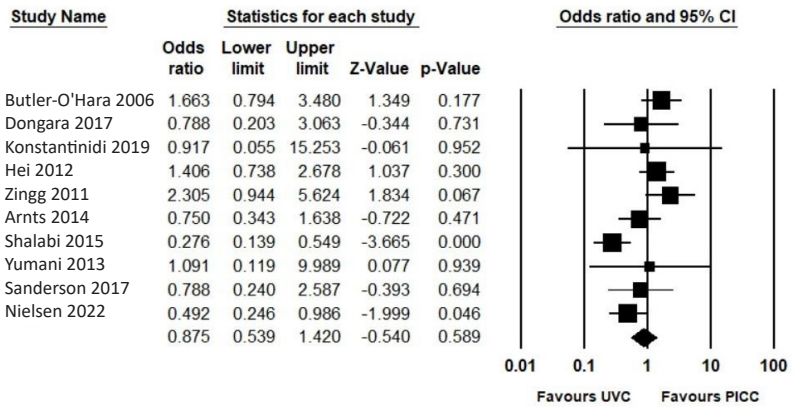

Figure 2. Forest plot of the studies included in the meta-analysis. Heterogeneity (I^2) = 61%; no evidence of publication bias (symmetrical funnel plot, 0.72 LFK index). CI=confidence interval; LFK=Luis Furuya-Kanamori; PICC=peripherally inserted central catheter; UVC=umbilical vein catheterization

RESULTS

The study selection process is shown in a flowchart in Figure 1. Based on the relevance to the research, 10 articles were selected for the systematic review and meta-analysis. Of the 10 research articles, 2 were RCTs,[20,21] 3 were prospective studies,[22–24] and 5 were retrospective studies (Table 1).[25–29] Research was limited to preterm infants admitted to level III neonatal care units or NICUs.

Based on the STROBE and CONSORT checklist results, most studies had a moderate risk of bias (six studies),[20,21,24,25,27,28] two studies[26,29] had a low risk of bias, and two studies[22,23] had a significant potential for bias.

Most studies revealed no significant differences in infection rates between UVC and PICC,[21–23,25] although

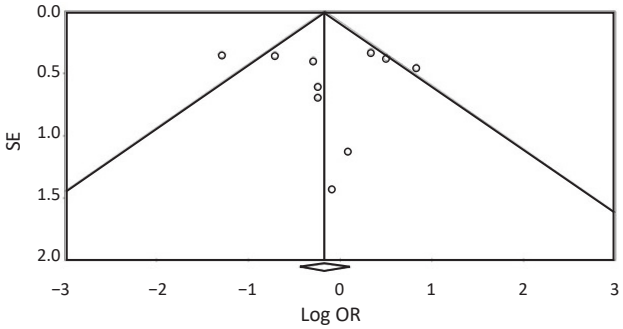

Figure 3. Funnel plot of the studies included in the meta-analysis. SE = 1.47, 95% CI: -2.97–3.82. CI=confidence interval; OR=odds ratio; SE=standard error

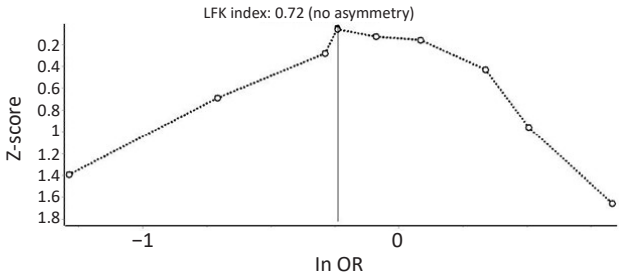

Figure 4. Doi plot of the studies included in the meta-analysis. LFK=Luis Furuya-Kanamori; OR=odds ratio

UVC was associated with less frequent late-onset sepsis.[26] However, higher incidence rates in the UVC group were observed for longer catheter days,[20,27] and only one study found a higher incidence rate of CLABSI for PICC than for UVC.[24] Additionally, using UVC and a longer duration of catheterization were the significant risk factors for CLABSI.[28,29]

A total of 3,962 UVCs and 2,922 PICCs (with 20,119 and 27,575 catheter days, respectively) were included in the meta-analysis. The proportion of newborns who developed CLABSI due to UVC was 5.91%, with a 95% CI spanning from 2.66–10.24. Of the 3,962 neonates with UVC, approximately 5.91% developed CLABSI.

The incidence rate was based on the overall number of CLABSI cases and the total number of catheter days across all studies in the meta-analysis. The combined incidence rate of CLABSI in the UVC group was 1.23 per 1,000 catheter days (95% CI: 1.00–1.51), showing an average of 1.23 CLABSI cases per 1,000 catheter days in the UVC group. Conversely, the pooled incidence rate of CLABSI in the PICC group was 3.03 per 1,000 catheter days (95% CI: 2.57–3.57), showing a higher average rate of CLABSI in this group.

The OR of developing CLABSI for newborns who received a UVC compared to those with a PICC was 0.88 (Figure 2). The pooled effect measure displayed moderate to high heterogeneity without publication bias. The funnel plot is symmetrical and the Doi plot showed an LFK index of 0.72, confirming the absence of publication bias; therefore, sensitivity analysis was not conducted (Figures 3 and 4).

DISCUSSION

CLABSI is a laboratory-confirmed BSI that occurs within 48 hours of central line insertion and is not related to infection at another site.[30] In the present study, the risk of developing CLABSI with either UVC or PICC was not significantly different. Therefore, meticulous sterilization techniques during catheter insertion are essential to prevent CLABSI. Healthcare providers should adhere to evidence-based practices, including hand hygiene, aseptic techniques, surveillance, and management strategies to reduce the risk of CLABSI. Our findings highlighted the significance of preventive measures in managing catheter-related BSI in preterm infants, considering that CLABSI can stem from multiple sources, such as organisms entering through the catheter site, contamination of the catheter hub, or even secondary infections.[30,31]

UVCs are pivotal in emergencies, particularly for neonates requiring immediate vascular access due to their rapid installation and practicality. However, physicians should not be deterred from using UVCs owing to potential infection concerns, given the urgency of the situations. Conversely, PICCs offer prolonged vascular access with minimal complications when managed correctly for neonates such as those with low birth weight (LBW) and without respiratory distress. Interestingly, the PICCs had a higher incidence rate of CLABSI than the UVCs, which could be attributed to the longer dwell time of PICC catheters. Prolonged catheter dwell time has been recognized as a significant risk factor for CLABSI progression.[32] Further investigations are warranted to better understand the factors contributing to the incidence of CLABSI in newborns with PICCs.

CLABSI risk has been associated with infant birth weight, which may be further compounded by the immature immunity of premature and LBW infants.[33,34] Additionally, several confounding factors, such as maternal infection and other underlying medical conditions, may also influence study outcomes.[35] It is important to note that studies reporting no association

between device dwell time and CLABSI risk may have certain constraints, such as small sample sizes and flawed study designs. Conversely, studies reporting a positive association between the catheter dwell time and CLABSI risk typically have a robust design, including large sample sizes, strict inclusion criteria, and proper catheter care bundles, including using ultrasound-guided insertion techniques. Sanderson et al[28] demonstrated a significant positive association between the catheter dwell time and CLABSI risk in a large sample size. Nielsen et al[29] also discovered that catheter dwelling time led to CLABSI in both the UVC and PICC groups, regardless of other factors. Moreover, Yumani et al[27] discovered that an extended period for which an umbilical catheter remains in place (7 days or more) was linked to a higher risk of developing CLABSI.

Longer dwell times for a central line may increase the potential for bacterial colonization at the insertion site or along the catheter track. Over time, organisms can migrate along the external surface of the catheter, especially in cases where sterile procedures are compromised or the catheter dressing becomes contaminated. Similar to other foreign bodies, catheters can act as substrates for biofilm formation. Biofilms are complex communities of microorganisms, particularly bacteria, embedded in a matrix of extracellular polymeric substances. Once a biofilm is established on the catheter surface, it can act as a reservoir for ongoing bacteremia, making it harder to treat and increasing the risk of CLABSI. Dwelling time indisputably influences the incidence of CLABSI.[36] Future research should consider other factors that may influence the risk of CLABSI, such as catheter insertion sites, maternal factors, and patient-related factors. Implementing a catheter replacement protocol may diminish the incidence of CLABSI in neonatal populations.

This study had a few limitations, including moderate to high heterogeneity of the pooled effect measures and variability in study quality. Although this review included three prospective studies and two RCTs, most of the studies were retrospective, which may limit the strength of the conclusions of the meta-analysis. Additionally, the procedure for inserting UVC and PICC was elucidated in the present study. Five studies[24,26–29] did not specify the personnel responsible for the procedure, while the other four studies[20–22,25] identified individuals such as trained neonatologists, NICU fellows, nurse practitioners, and resident physicians responsible for catheter placement. Furthermore, Hei et al[23] indicated that catheter insertion was the responsibility of a neonatologist, while the subsequent daily care was managed by senior NICU nurses. There was also extensive diversity in the types of catheter devices employed, influenced by different specifications and quality standards. Additionally, the included studies were conducted in diverse nations with varying healthcare systems and policies, which may restrict the generalizability of the results to other settings. The heterogeneity (I^2 = 61%) observed in the meta-analysis might not allow for drawing definitive conclusions about the differences in the incidence rate of CLABSI between UVCs and PICCs.

In conclusion, CLABSI may further complicate the preexisting vulnerability of preterm infants undergoing catheterization for health complications. Based on the pooled results, the incidence rate of CLABSI was lower in the array using UVCs than in the array using PICCs, and the odds of developing CLABSI were 12% lower in infants who received UVC than in those who received a PICC; however, the difference was not statistically significant. While this review provided valuable insights into the incidence of CLABSI related to UVCs and PICCs in preterm infants, the predominance of retrospective studies highlights the need for additional prospective studies to validate and extend these results.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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