

STUDI E RICERCHE

Relationship between peripheral insertion site and catheter-related phlebitis in adult hospitalized patients: a systematic review

Relazione tra sito anatomico di inserimento del catetere venoso periferico e flebite catetere correlata nei pazienti adulti ospedalizzati: una revisione sistematica.

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ABSTRACT

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AIM. To explore the relationship between the anatomical site of peripheral venous catheterization and risk of catheter-related phlebitis.

BACKGROUND. Peripheral venous catheterization is frequently associated with phlebitis. Recent guidelines, recommend the use of an upper-extremity site for catheter insertion but no univocal consensus exists on the anatomical site with lower risk of phlebitis.

Design. Systematic review.

METHODS: We searched Medline (PubMed) and CINAHL (EBSCOhost) databases until the end of January 2017. We also reviewed the reference lists of retrieved articles and gray literature was excluded. Searches were limited to articles published in English with no restriction imposed to date of publication. The primary outcome was the incidence of phlebitis associated with anatomical site of peripheral catheterization. We included randomized controlled trials and observational studies on adult patients who required a peripheral catheter for the administration of medication, intermittent or continuous fluid infusion.

RESULTS. Antecubital fossa veins are associated with lower phlebitis rates, while hands veins are the most risky sites to develop phlebitis. There is no consensus regarding vein in forearm.

CONCLUSION. Choosing the right anatomical site to insert a peripheral venous catheter is important to decrease phlebitis rate. Further studies should compare indwelling time in different anatomical sites with phlebitis rate. A more standardized approach in defining and assessing phlebitis among studies is recommended.

KEY WORDS: systematic review, phlebitis, peripheral venous catheterization, anatomical sites.

RIASSUNTO

OBIETTIVO. Esplorare la relazione tra il sito anatomico di inserimento del catetere venoso periferico e il rischio di flebite correlata.

INTRODUZIONE. Il cateterismo venoso periferico è spesso associato a flebiti. Linee Guida recenti raccomandano l'utilizzo delle vene degli arti superiori per l'inserimento del catetere ma non esiste univoco consenso circa il sito anatomico correlato al minor rischio di sviluppare flebite.

METODI. Abbiamo effettuato una revisione sistematica della letteratura consultando i database Medline (PubMed) e CINAHL (EBSCOhost) fino al termine del mese di Gennaio 2017. Inoltre, abbiamo revisionato le citazioni bibliografiche degli articoli reperiti e la letteratura grigia è stata esclusa. Sono stati ricercati articoli pubblicati in lingua inglese, senza limiti posti per la data di pubblicazione. Abbiamo incluso: gli studi che riportavano dati sui tassi di flebite associati al sito anatomico di cateterismo periferico; gli studi clinici randomizzati controllati e gli studi osservazioni condotti su pazienti adulti che necessitavano dell'inserimento di un catetere venoso periferico per la somministrazione intermittente o continua di liquidi e farmaci.

RISULTATI. L'inserimento del catetere venoso periferico nelle vene della fossa antecubitale è associato ad un minor tasso di flebiti, mentre le vene della mano sono il sito a maggior rischio di sviluppare flebite. Non esiste consenso circa le vene dell'avambraccio.

CONCLUSIONI. La scelta del sito anatomico corretto per l'inserimento di un catetere venoso periferico è importante per diminuire i tassi di flebite. Ulteriori studi dovrebbero comparare i tassi di flebite associati al tempo di permanenza dei cateteri venosi periferici inseriti in differenti siti anatomici. Si raccomanda, inoltre, un approccio maggiormente standardizzato nella definizione e valutazione del grado di flebite all'interno dei diversi studi.

PAROLE CHIAVE: revisione sistematica, flebiti, cateterismo venoso periferico, siti anatomici.

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INTRODUCTION

Peripheral venous catheters (PVCs) are the most frequently used intravenous devices for medication, fluids and blood components administration in hospitalized patients (Mermel et al., 2001). However, even though PVCs rarely cause systemic complications (Maki et al., 2006), they are frequently associated with phlebitis, catheter-related infections and obstructions (Maki & Ringer, 1991; Bregenzer et al., 1998; White, 2001; Cornely et al., 2002; Karadeniz et al., 2003; Webster et al., 2007; Uslusoy & Mete, 2008; Cicolini et al., 2009; Lee et al. 2009; Forni et al., 2010; do Rego Furtado, 2011; Mestre Roca et al., 2012). These complications could lead to catheters removal, and insertion of a new catheter in a different anatomical site (Tagalakis, 2002).

Several authors showed that phlebitis is the most frequently PVC-related complication (Zingg & Pittet, 2009) and it is estimated that between 20% and 80% of hospitalized patients who required peripheral intravenous therapy develop phlebitis (Panadero et al., 2002).

Authors showed that the risk of phlebitis could be influenced by different factors such as catheter material (Madan, 1992; Gaukgroger, 1988) and size (Maki & Ringer, 1991), indwelling time (Tager, 1983; Maki & Ringer, 1991; Lai, 1998) type of infusate (Melly, 1975; Sheth, 1983; Maki & Ringer, 1991; Raad, 1994; Webster, 2010; O'Grady et al., 2011) and patient-related risk factors such as thrombophilic predisposition, high haemoglobin levels and poor veins' quality (Zingg & Pittet, 2009). It has been widely acknowledged that peripheral catheterization may be associated with phlebitis rate (Maki & Ringer, 1991; Bregenzer et al., 1998; White, 2001; Cornely et al., 2002; Karadeniz et al., 2003; Webster et al., 2007; Uslusoy & Mete, 2008; Cicolini et al., 2009; Lee et al., 2009; Forni et al., 2010; do Rego Furtado, 2011; Mestre Roca et al., 2012, Cicolini et al., 2014). However, with regard to PVCs sites of insertion, Centers for Disease Control and Prevention (CDC) Guidelines, recommend only to use upper-extremity site for peripheral catheterization, but no further specification is provided regarding the proper anatomical site of insertion (O'Grady, 2011).

To date, there are no systematic reviews summarizing results on the influence of anatomical site of PVC insertion on phlebitis rate. Therefore, a systematic synthesis of the available evidence could be useful to support decision making in clinical practice.

THE REVIEW

Aim

The aims of this systematic review are: (1) synthesized the best available evidence on the relationship

between the anatomical site of PVCs insertion and phlebitis rate; (2) identify gaps in existing literature to make recommendation for further research.

One research question guided this systematic review:

- Which is the anatomical site of PVCs insertion in adult hospitalized patients, with lower risk of phlebitis?

Design

A systematic review was performed according to the methods described by Higgins & Green (2011).

Search methods

Databases and search terms

A literature review was performed in the following electronic databases: Medline (through PubMed), and CINAHL (through EBSCOhost) until the end of January 2017. Searches were limited to articles published in English and no restrictions were imposed to date of publications. Gray literature was excluded. In addition, we reviewed the reference lists of retrieved articles to identify all relevant studies.

As each database has its own indexing terms, different search strategies were developed for MEDLINE, CINAHL databases (Table 1).

The MeSH terms "Catheters, Indwelling/adverse effects", "Catheterization, Peripheral" and "Phlebitis" combined with the free text terms: (OR) "peripheral venous cannulae", (NOT) "central catheter" (using filters: Languages English; Adult 19+ years) were used to search MEDLINE (PubMed) database.

For the CINAHL database the boolean terms "Catheterization, Peripheral" AND "phlebitis" NOT "pediatric" were used and were run under the major heading "phlebitis"

Figure 1 shows the search and retrieval process.

Inclusion/exclusion criteria

We used pre-defined criteria to include all relevant articles in this review. Studies were included if they fulfilled the following inclusion criteria: (I) randomized controlled trial (RCT) or observational studies; (II) studies reporting data on the phlebitis rate (using any definition identified by the authors) as primary or secondary outcome; (III) population: adult patients who required a PVC for the administration of medication, intermittent or continuous fluid infusion.

We excluded: (I) studies measuring PVC-related complication but not phlebitis; (II) studies performed in paediatric setting; (III) studies on PVC placed for the administration of blood components; (IV) studies not published in English and (V) duplicate articles.

Two authors conducted an initial screening of titles and abstracts to identify all potentially relevant articles according to the review question. Then, each abstract

Table 1. Search strategies.

<p>DATABASE: Medline (PubMed)</p> <p>1. MeSH terms: Catheterization, Peripheral. Free text terms: catheter phlebitis. Filters: Adult 19+ years; Languages English. Search details: (("catheters"[MeSH Terms] OR "catheters"[All Fields] OR "catheter"[All Fields]) AND ("phlebitis"[MeSH Terms] OR "phlebitis"[All Fields]) AND ("catheterization, peripheral"[MeSH Terms] OR ("catheterization"[All Fields] AND "peripheral"[All Fields]) OR "peripheral catheterization"[All Fields] OR ("catheterization"[All Fields] AND "peripheral"[All Fields]) OR "catheterization, peripheral"[All Fields])) AND (English[lang] AND "adult"[MeSH Terms]). Search results: items 149.</p> <p>2. MeSH terms: Catheterization, Peripheral; phlebitis; Catheters, Indwelling/adverse effects. Free text terms: peripheral venous cannulae, peripheral inserted central catheter. Filters: Adult 19+ years; Languages English. Search details: "catheters, indwelling/adverse effects"[Mesh Terms] AND ("catheterization, peripheral"[MeSH Terms] OR ("catheterization"[All Fields] AND "peripheral"[All Fields]) OR "peripheral catheterization"[All Fields] OR ("catheterization"[All Fields] AND "peripheral"[All Fields]) OR "catheterization, peripheral"[All Fields]) OR (peripheral[All Fields] AND ("veins"[MeSH Terms] OR "veins"[All Fields] OR "venous"[All Fields]) AND ("cannula"[MeSH Terms] OR "cannula"[All Fields] OR "cannulae"[All Fields])) AND ("phlebitis"[MeSH Terms] OR "phlebitis"[All Fields]) NOT (peripheral[All Fields] AND inserted[All Fields] AND central[All Fields] AND ("catheters"[MeSH Terms] OR "catheters"[All Fields] OR "catheter"[All Fields])) AND "adult"[MeSH Terms]. Search results: items 44.</p> <p>3. MeSH terms: Catheterization, Peripheral; Catheters, Indwelling/adverse effects. Free text terms: peripheral venous cannulae; catheter phlebitis. Filters: Adult 19+ years; Languages English. Search details: ("catheterization, peripheral"[MeSH Terms] OR ("catheterization"[All Fields] AND "peripheral"[All Fields]) OR "peripheral catheterization"[All Fields] OR ("catheterization"[All Fields] AND "peripheral"[All Fields]) OR "catheterization, peripheral"[All Fields]) OR (peripheral[All Fields] AND ("veins"[MeSH Terms] OR "veins"[All Fields] OR "venous"[All Fields]) AND ("cannula"[MeSH Terms] OR "cannula"[All Fields] OR "cannulae"[All Fields])) AND ("catheters"[MeSH Terms] OR "catheters"[All Fields] OR "catheter"[All Fields]) AND ("phlebitis"[MeSH Terms] OR "phlebitis"[All Fields])) AND "catheters, indwelling/adverse effects"[Mesh Terms] AND "adult"[MeSH Terms]. Search results: items 38.</p>
<p>DATABASE: CINAHL</p> <p>1. BOOLEAN TERMS: Catheterization, Peripheral AND phlebitis. Search results: 146 title and abstract.</p> <p>2. BOOLEAN TERMS: Catheterization, Peripheral AND phlebitis NOT pediatric. Search results: 133 title and abstract. Narrow by SubjectMajor – "phlebitis": 48 title and abstract.</p>

identified as relevant in the initial selection, was examined independently. The full text of all abstracts selected were reviewed on the basis of inclusion criteria.

Disagreements were resolved by discussion and if it persisted, a third author was involved for a final decision and the process ended with all authors' consensus. All information about study results were obtained from the published articles. If required, authors of all eligible studies were contacted through e-mail to obtain missing information or clarify any ambiguity throughout the paper.

Data abstraction

For each studies, two independent authors extracted the following main sets of data:

- Authors, Journal and publication year;
- country where the study was conduct and study setting;
- study design and aim(s);
- main results;
- definitions of phlebitis

Quality appraisal

The methodological quality of the included studies

was assessed using standardized checklists. The Scottish Intercollegiate Guidelines Network (SIGN) checklist was used to assess controlled trials studies (SIGN, 2001). This checklist assesses the overall methodological quality of the articles classifying the studies in the following categories: (I) High quality: majority of criteria met, little or no risk of bias, results unlikely to be changed by further research; (II) Acceptable: most criteria met, some flaws in the study with an associate risk of bias, conclusion may change in the light of further studies; (III) Low quality: most criteria not met or significant flaws relating to key aspects of study design, conclusion likely to change in the light of further studies.

As no accepted gold standard tool for assessing quality of observational epidemiological studies exist (Sanderson et al. 2007), we used an adapted version of "Quality assessment checklist for observational studies (QATSO Score)" developed by Wong and colleagues (2008). This tool included 4 items, scored as 0 (=not met) or 1 (=met), to assess and score the following aspects: external validity, reporting, bias and confounding. The total score was calculated by dividing total number of all applicable items, and the articles were classified into three categories:

"good" quality (67% or more in the score); "fair" quality (34–66%) and "poor" quality (below 33%).

RESULTS

The electronic database search yielded 191 abstracts and titles. Following removal of not relevant studies ($n=139$), the potentially eligible studies were screened and 43 articles were excluded.

Quality assessments were completed on nine studies that were all included in the final review (Figure 1).

Characteristics of included studies

The nine studies included in the review were published between 1991 and 2016. Seven studies were obser-

vational in design (Bregenzler et al., 1993; Karadenitz et al., 2003; Uslusoy & Mete, 2008; Cicolini et al., 2009; do Rego-Furtado, 2011; Cicolini et al., 2014; Urbanetto et al., 2016). Only two study was a randomized controlled trial (Maki & Ringer 1991; Wallis et al., 2014).

Studies were performed in Switzerland (Bregenzler et al., 1993), Portugal (do Rego-Furtado, 2011), Turkey (Karadenitz et al., 2003, Uslusoy & Mete, 2008), Italy (Cicolini et al., 2009, Cicolini et al., 2014), Brazil (Urbanetto et al. 2016), USA (Maki & Ringer 1991) and Australia (Wallis et al., 2014).

Of these researches, only two were multicenter in design (Cicolini et al., 2014; Wallis et al., 2014). Two studies (Uslusoy & Mete, 2008; do Rego-Furtado, 2011) were carried out only in general surgery inpatient units of a University Hospital and a Local

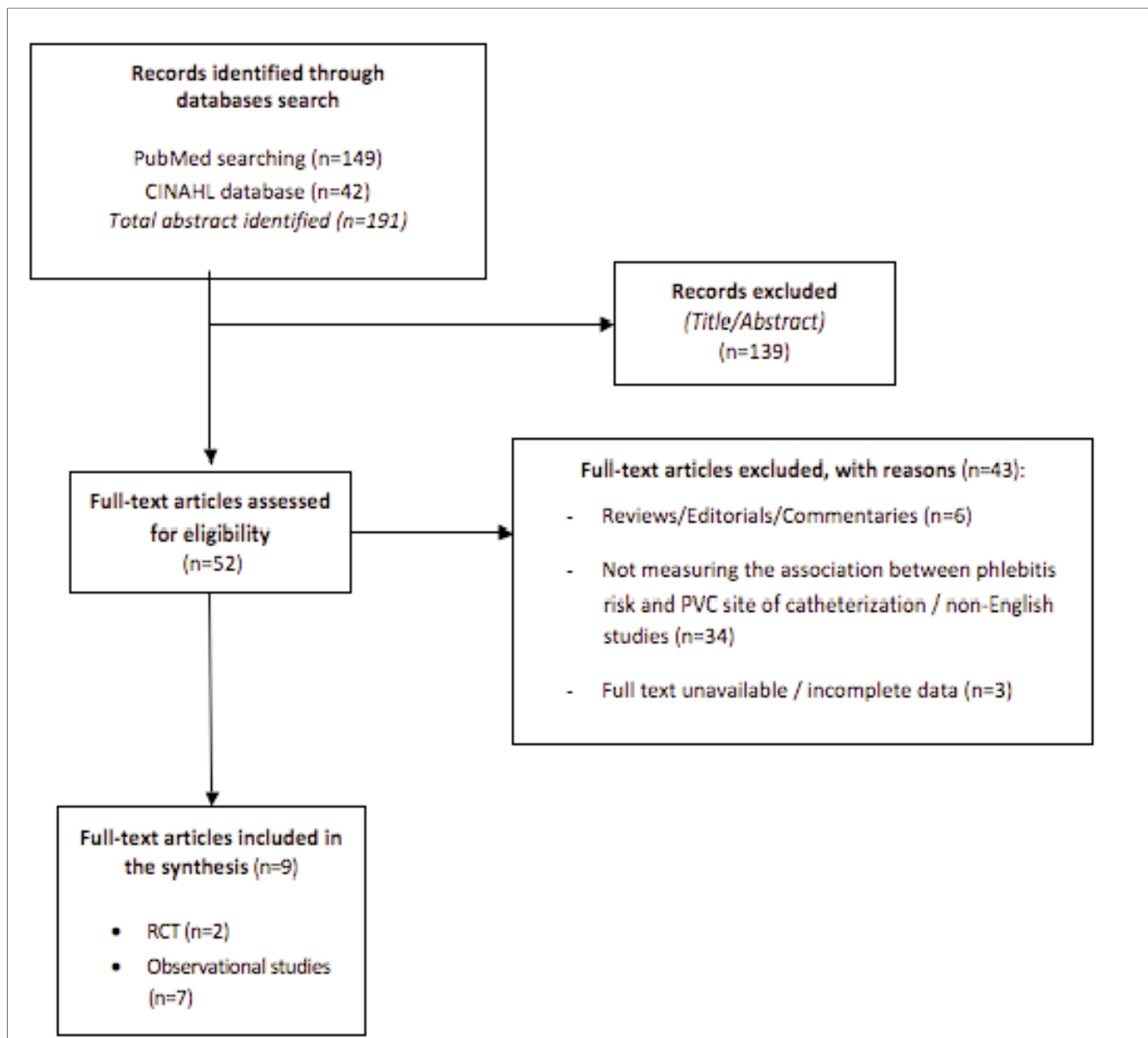


Figure 1. Search strategy and studies selection.

Hospital. Five studies collected data in internal medicine Departments (Maki & Ringer, 1991, Bregenzner et al., 1993, Karadenitz et al., 2003, Cicolini et al., 2009; Cicolini et al., 2014) or in both medical and surgical units (Cicolini et al., 2009; Cicolini et al., 2014; Wallis et al., 2014); three of these studies was carried out also in obstetrics and gynecology units (Karadenitz et al., 2003, Cicolini et al., 2009; Cicolini et al., 2014), in geriatrics and cardiology, general surgery, orthopaedics and other surgical units (Cicolini et al., 2014). The study of Urbanetto et al. (2016) was carried out in a clinical hospitalization service of a University Hospital in the city of Porto Alegre (Brazil), however, authors did not specify the units in which data were collected. Table 2 shows the characteristics of the studies and the overall scores of quality assessment for each study included in this review.

Incidence of phlebitis

Results on the relationship between the anatomical site of PVC insertion and phlebitis' risk varied across studies (Table 3). Only two studies compared, as their main aim, the relationship between different anatomical sites and incidence of phlebitis, showing antecubital fossa veins (Cicolini et al., 2009; Cicolini et al., 2014) or forearm veins (Cicolini et al., 2014) as the safest sites for cannulation. In particular, results of these researches (Cicolini et al., 2009; Cicolini et al., 2014) showed that phlebitis were statistically significantly higher in patients with PVC inserted on the dorsal side of the hand compared to the cubital fossa veins (OR:3.33, CI:1.37–8.07, $P<0.001$; OR:0.66, CI:0.46–0.95, $P<0.05$, respectively) or forearm veins (OR:0.52, CI:0.32–0.84, $P<0.05$) (Cicolini et al., 2014). In addition, the study of Wallis et al. (2014) showed forearm veins as the safest sites for PVCs insertion, reporting findings on the association between phlebitis and catheter insertion in the wrist or upper arm compared to hand, antecubital fossa and forearm; however, this association was not statistically significant. Other studies which investigated phlebitis' risk factors, showed antecubital fossa as favored site in order to minimize phlebitis' risk (Cornely et al., 2002) and suggested an increased risk when (dorsum of the) hand veins were used (Maki & Ringer, 1991; Curran et al., 2000; Lee et al., 2009; Forni et al., 2010). Contrary, other authors reported forearm (Bregenzner et al., 1993, Karadenitz et al., 2003) or antecubital fossa (Uslusoy & Mete, 2008, do Rego-Furtado, 2011) veins as the sites with higher incidence of phlebitis. In particular, Bregenzner and colleagues (1998) showed that forearm vein is the most frequently site used for PVC insertion with a total of 103 phlebitis occurred on a total of 467 inserted catheters. Uslusoy & Mete (2007) showed

higher incidence of phlebitis when PVC was inserted in antecubital fossa (63.2%) ($p = 0.049$) veins compared to forearm, dorsum of the hand and wrist veins. In addition, Maki e Ringer (1991) identified forearm veins as the anatomical site associated with higher risk for phlebitis development, whereas wrist resulted the site with lower phlebitis' risk. However, even if this results comes from a study with a quite large sample size and with a robust methodology; we have to take into account that the study was monocentric in design and the evidence is quite old; in the last 25 years many things about the management of PVCs are changed (e.g. material, antiseptic techniques) and nurses' knowledge and skills on catheters' care have been up to date and based on recent evidence in order to reduce the complications associated with cannulation of peripheral veins. It is interesting to note that only the study of Urbanetto et al. (2016) analysed the incidence of phlebitis while using and following the removal of PVC (post-infusion phlebitis) highlighting that the puncture of forearm veins was associated with post-infusion phlebitis ($p = 0.054$). However, this result should be evaluated taking into account that only 1.9% of the PVC were located in forearm veins. Therefore, findings from the included studies have produced contradictory results and there is no consensus regarding the insertion of PVCs in forearm veins as the the safest sites for cannulation.

Phlebitis evaluation tools

The studies included in this review used different tools to evaluate Phlebitis degree.

Two studies (Maki & Ringer, 1991; Bregenzner et al., 1993) used a phlebitis definition but not a phlebitis assessment scale: in Maki & Ringer (1991) catheter site was quantitatively scored for pain (0,1), tenderness (0 to 2), erythema (0 to 2), purulence (0,1), swelling (0 to 2) and a palpable cord (0,1), whereas, Bregenzner et al. (1993) classified phlebitis by the presence of at least 2 of the following signs or symptoms on examination of the catheter insertion site: redness, swelling, palpable venous cord, tenderness, or pain, as in the study of Maki & Ringer (1991). Wallis and colleagues (2014) used a similar classification; phlebitis was defined as the simultaneous presence of two or more of the following signs or symptoms: tenderness and/or pain (0-10-point scale); erythema extending to at last 1 cm to the insertion site; swelling extending to at last 1 cm to the insertion site; purulent discharge from the insertion site and a palpable venous cord beyond the tip of the PVC. The study of Urbanetto et al. (2016) did not specify if a phlebitis assessment scale was used or the criteria used to diagnose and classify phlebitis' severity.

The Scale of Phlebitis, developed by Intravenous

Table 2. Characteristics of included studies.

Author(s) (year)	Design	Sample	Setting	Aim(s)	Phlebitis evaluation tool	Quality assessment: total score
do Rego Furtado (2011).	Descriptive, observational. Monocentric study.	171 patients, 286 catheters.	A general surgery department, one General Hospital in Portugal.	To determine the incidence of phlebitis associated with peripheral cannula in a general surgery department, and the factors, which are potentially associated with its development.	VIP Scale (Jackson, 1998). Degrees of phlebitis 0-5.	QUATSO score: 40% (fair/acceptable quality).
Cicolini et al. (2009).	Observational. Monocentric study.	427 patients, 427 catheters.	Surgical, medical, obstetrics and gynaecology units, one General Hospital in Italy.	To investigate the most suitable anatomical site of insertion of peripheral venous cannula to reduce incidence of thrombophlebitis.	Checklist to diagnose and classify phlebitis' severity published in previous studies (Lundgren et al. 1993). Degrees of phlebitis 0-5.	QUATSO score: 60% (fair/acceptable quality).
Uslusoy & Mete (2008).	Descriptive comparative study. Monocentric study.	355 patients, 568 catheters.	General surgery inpatient unit, one University Hospital in Turkey.	To investigate the predisposing factors in the development of phlebitis.	The Scale of phlebitis of the Infusion Nurses Society (Infusion Nursing Standards of Practice, 2000). Degrees of phlebitis 0-4.	QUATSO score: 20% (bad/low quality).
Karadeniz et al. (2003).	Observational. Monocentric study.	58 patients, 58 catheters.	Internal, surgical, obstetrics and gynaecology units, one Hospital in Turkey.	To determine the knowledge of nurses about using intravenous catheters and the symptom and treatment procedures for phlebitis.	Unspecified.	QUATSO score: 40% (fair/acceptable quality).
Bregenzer et al. (1998).	Observational. Monocentric study	451 patients, 665 catheters.	Internal medicine, surgical and medical intensive care units (ICUs), one University Affiliated Tertiary Care Center, Switzerland.	To evaluate the day-specific risk for phlebitis, catheter infection and obstruction with peripheral intravenous catheters left in place as long as clinically indicated.	A quantitative scoring scale used in a previous study (Maki & Ringer, 1991) and based on the presence of two or more of the following signs or symptoms: pain, tenderness, erythema, swelling, purulence, palpable venous cord.	QUATSO score: 40% (fair/acceptable quality).
Maki & Ringer (1991).	Randomized Controlled Trial (RCT). Monocentric study.	1054 catheters.	Medical, surgical and intensive care units (ICUs), one University Hospital, Wisconsin, USA.	To explore risk factors for infusion-related phlebitis with peripheral venous catheters.	A quantitative scoring scale based on the presence of two or more of the following signs or symptoms: pain, tenderness, erythema, swelling, purulence, palpable venous cord.	SIGN checklist: high quality (++)
Cicolini et al. (2014).	Observational. Multicenter study.	1498 patients, 1498 catheters.	Internal medicine, geriatrics, cardiology, general surgery, orthopaedics, obstetrics & gynaecology, other surgical units, five Italian Hospital of three different regions.	The primary objective was to evaluate whether PVC site of insertion influences the risk of catheter-related phlebitis. Secondary objectives were to explore other potential predictors of phlebitis (time in situ, i.e. duration between insertion and removal)	Visual Infusion Phlebitis (VIP) score (Gallant & Schultz 2006) with grades of severity from 1-5.	QUATSO score: 80% (good/high quality).
Wallis et al. (2014)	Randomized Controlled Trial (RCT). Multicenter study.	3283 patients, 5907 catheters.	Medical and surgical units, two large Metropolitan Hospitals and one large Regional Hospital, Queensland, Australia.	To assess the relative importance of risk factors for PVCs failure.	A quantitative scoring scale based on the presence of two or more of the following signs or symptoms: pain, tenderness, erythema, swelling, purulence, palpable venous cord.	SIGN checklist: high quality (++)
Urbanetto et al. (2016).	Observational (Cohort study). Monocentric study.	171 patients, 361 catheters.	A Clinical Hospitalization Service, one University Hospital, city of Porto Alegre (Brazil); units: unspecified.	To explore the incidence of phlebitis and the association between risk factors and the incidence of phlebitis while using and following the removal of post-infusion phlebitis in hospitalized adults.	Unspecified.	QUATSO score: 40% (fair/acceptable quality).

Table 3. Phlebitis incidence rates as reported in the included studies.

Author	Overall	Wrist	Hand	Forearm	Antecubital fossa	Arm	P-value and statistics*
Rego Furtado (2011).	171/286 (61.5%)	27/51 (52.9%)	32/63 (50.8%)	52/91 (57.1%)	60/72 (83.3%)	5/9 (55.6%)	(Pearson $\chi^2= 19.995$, $df=4$, $p<0.001$). Anatomic region (forearm=0, others=1): ($\beta=0.071$, $p=0.809$, OR:1.074, CI 0.601-1.918).
Cicolini et al. (2009).	276/427 (64.6%)	-	37/44 (75.0%)	113/182 (62.1%)	126/201 (62.7%)	-	($\beta=0.071$, $p=0.809$, OR:1.074, CI 0.601-1.918). Hand:cubital fossa (OR:3.33;CI: 1.37–8.07) $p=0.000$. Forearm:cubital fossa (OR: 0.83; CI: 0.53-1.30) $p=0.42$.
Uslusoy & Mete (2008).	309/568 (54.5%)	56/115 (48.7%)	75/154 (48.7%)	99/174 (56.9%)	79/125 (63.2%)	-	($\chi^2=7.864$, $df = 3$, $p= 0.049$).
Karadeniz et al. (2003).	39/58 (67.2%)	8/13 (20.5%)	10/16 (25.6%)	12/16 (30.8%)	9/13 (23.8%)	-	($\chi^2= 0.032$, $p<0.05$).
Bregenzer et al. (1998).	102/451 (22.6%) first catheter; 18/158 (11.4%) subsequent catheter.	-	14/122 (11.5%)	103/467 (22.0%)	-	-	HR: 0.09
Maki & Ringer (1991).	441/1.054 (41.8%)	-	-	-	-	-	Hand:forearm (RR=0.71; CI: 0.50-1.00) $p=0.053$. Wrist:forearm (RR=0.60; CI: 0.41-0.88) $p=0.010$. Other:forearm (RR=0.68; CI: 0.34-1.36) $p>0.2$.
Cicolini et al. (2014).	231/1.498 (15.4%)	-	65/341 (19.0%)	101/646 (15.5%)	66/511 (12.9%)	-	Dorsum of the hand:antecubital fossa (OR=0.66; CI:0.46–0.95) $p=0.026$. Dorsum of the hand:forearm veins (OR=0.52; CI:0.32–0.84) $p=0.008$.
Wallis et al. (2014).	273/5.907 (4.6%)	47/273 (17.3%)	41/273 (15%)	41/273 (15%)	43/273 (15.8%)	55/273 (20.1%)	Wrist:forearm (IRR=1.15; CI: 0.63-1.96) $p >0.05$. Hand:forearm (IRR=1.00; CI: 0.71-1.39) $p >0.05$. Upper arm:forearm (IRR=1.34; CI: 0.86-2.01) $p >0.05$. Antecubital fossa:forearm (IRR=1.05; CI: 0.70-1.55) $p >0.05$.
Urbanetto et al. (2016).	Overall phlebitis: 76/361 (21%) Phlebitis while using PIC: 36/361 (10%) Post-infusion phlebitis: 40/361 (11%)	Overall phlebitis: Arm/wrist 46/361 (12.7%) Phlebitis while using PIC: 22/178 (11%) Post-infusion phlebitis: 24/176 (12%)	Overall phlebitis: 19/361 (5.3%) Phlebitis while using PIC: 10/81 (11%) Post-infusion phlebitis: 9/82 (9.9%)	Overall phlebitis: 4/361 (1.1%) Phlebitis while using PIC: 1/6 (14.3%) Post-infusion phlebitis: ¼ (42.9)	Overall phlebitis: 7/361 (1.9%) Phlebitis while using PIC: 3/60 (4.8%) Post-infusion phlebitis: 4/59 (6.3%)	-	- No statistically significant associations: $p=0.054$. PIC in the forearm was associated with post-infusion phlebitis ($p = 0.054$).

*comparing different anatomical insertion sites.

Nurses Society (INS), was used to diagnose phlebitis (INS, 2000) by Uslusoy & Mete (2008). Phlebitis Scale (from the Infusion Nursing Standards of Practice, 2011) identified 4 grades as follow: Grade 0 – No symptoms, Grade 1 – Erythema at access site with or without pain, Grade 2 – Pain at access site with erythema and/or edema,

Grade 3 – Pain at access site with erythema and/or edema, streak formation, palpable venous cord. Grade 4 – Pain at access site with erythema and/or edema, streak formation, palpable venous cord greater than 1 in length; purulent drainage.

Cicolini et al. (2009) used the checklist published in

Lundgren and colleagues (1993) defining phlebitis as follows: Degree 0 – No complications: none or slight discomfort; tenderness at insertion; Degree 1 – Slight thrombophlebitis: redness and tenderness; Degree 2 – Medium thrombophlebitis: redness, tenderness, pain and slight swelling; Degree 3 – Severe thrombophlebitis: redness, tenderness, pain, swelling more than 24 cm, increased temperature in the area and palpable cord in the vein; Degree 4 – Very severe thrombophlebitis: redness, pain, swelling more than 5 · 8 cm, increased temperature in the area, palpable cord in the vein, pain spreading up to the arm, red line and possibly fever.

The Standardized Visual Infusion Phlebitis (VIP) scale (0 to 5) to diagnose and classify phlebitis' severity, developed by Jackson (1998) was used in do Rego-Futado (2011). The score range from 0 indicating no symptom of phlebitis, to 5 with sign of purulent drainage, redness, and a palpable cord greater than 3 inches.

Karadenitz et al. (2003) did not declared the Scale they used.

Cicolini et al. (2014) classified the infusion related phlebitis implementing the modified Visual Infusion Phlebitis score (VIP) proposed by Gallant & Schultz (2006) with grades of severity from 1-5.

DISCUSSION

This systematic review aimed to evaluate the safety of anatomical site for PVC insertion in adult hospitalized patients. Phlebitis incidence related to anatomical site of PVC insertion, widely varied across included studies because of difference in study design, duration of follow-up, patients selection and characteristics, definition of anatomical sites for peripheral catheterization, time in situ of catheters and definition of phlebitis degree. Although all authors used published and widely accepted tools to evaluate phlebitis degree, they used different criteria for defining "phlebitis". However, these heterogeneous results could be due to the absence of a universally validated scale with strong reliability; in fact, validity and reliability data have not been established for most of the scales (Ray-Barruel et al., 2014). Moreover, another possible source for heterogeneity of phlebitis rate may be related to in-patient location or hospital ward. This could be associated with several factors such as the presence of underlying medical conditions (e.g. cancer, immunodeficiency) or surgical patient-specific risk factors, as highlighted in the study conducted by Cicolini et al. (2014) where the probability of having phlebitis was lower for patients admitted to general surgery and orthopaedics wards compared with those admitted to the medical units (ORs 0.61 and 0.51, respectively; both $P < 0.05$), while Lee et al. (2009) and Mestre Roca et al. (2012) found an increased risk of developing phlebitis associated with

medical wards, as opposed to those surgical.

Moreover, the use of the upper extremities for peripheral catheterization in adult patients is recommended by current guidelines with no specification of preferred anatomical site (O'Grady et al., 2011), however, the site of catheterization should be selected avoiding any bony prominences and areas of joints flexion that could facilitate movements of the cannula within the vein lumen (Higginson, 2011). Despite this evidence, in everyday clinical practice, health professionals often choose anatomical site for catheterization on the basis of personal experience (Maki & Ringer, 1991; Mermel et al., 2001), habits, preferences and other factors such as the quality of veins. It is considered easier to insert PVCs in large vessels even if is recognized that PVCs placed in an area of joint flexion may lead to a blood flow reduction with a probable damage of catheters and thus, an increased risk of phlebitis as result (Angels & Barbone, 1994). This could be a possible explanation for the higher rate of phlebitis in the antecubital fossa reported by authors (Maki & Ringer, 1991; Bregenzer et al., 1998; White, 2001; Cornely et al., 2002; Karadeniz et al., 2003; Webster et al., 2007; Uslusoy & Mete, 2008; Cicolini et al., 2009; Lee et al., 2009; Forni et al., 2010; do Rego Furtado, 2011; Mestre Roca et al., 2012). Another possible risk-factor for phlebitis could be the insertion of PVC in emergency conditions, where operator insert venous access as quick as possible, with possible impact on aseptic procedures (Tomford et al., 1984; Soifer et al., 1998; Maki & Ringer, 1991; Webster et al., 2015).

This review found no univocal results of benefit for a specific site of insertion with respect to all other sites and highlight the need to carried out more studies aimed to analyze the relationship between different anatomical sites and incidence of phlebitis. In particular, it would be important to carry out more studies to analyze the association between phlebitis incidence and anatomical site of catheterization as a primary study aim. Moreover, to better understand and compare results from different studies, authors should report a well-defined classification of the anatomical site for PVC insertion and a univocal definition of phlebitis degree.

Overall assessment of quality

Overall, the methodological quality of the studies was good (quality rating from acceptable to high); only one study has received a lower score (Uslusoy & Mete, 2008), however, considering the few studies available in the literature on the relationship between the anatomical site of PVC insertion and phlebitis rate, we decided to include this study in the final review.

In the most of studies the methods section was clearly described. A limitation, common to the majority of the included studies concerns the adequacy of the study

sample; in fact only two studies (Maki & Ringer, 1991; Cicolini et al., 2014) have reported in the methods section a paragraph on the sample size estimation.

Another aspect that could have affected the methodological quality of the studies included in this review, concerns the ethical considerations; in fact, authors have declared that informed consent was obtained from all participants, but only three studies (Cicolini et al., 2009; Cicolini et al., 2014; Wallis et al., 2014) have reported the approval of the study protocol by an ethics committee.

Review strengths and limitations

Our review have several limitations about the strength of conclusions that can be drawn from our results. Firstly, the limited number of original research focused on the topic hampered the results of the review. Second, only two studies used a RCT study design, while other studies were observational in design and this factor could decrease the generalizability of results. Moreover, we included only available full text articles published in English and the applied search strategy could have missed to identify other relevant and different studies' results. However, we performed a careful literature research and we clearly described the method to prevent potential biases in the review process and to ensure the results' reproducibility. In addition, older studies might have higher rates because of the more risky materials used compared with newer catheters. Our review did not consider indwelling times compared to the insertion site, so it is not possible to suggest which insertion sites are better in order to postpone phlebitis and to enhance catheter duration.

CONCLUSION

Phlebitis is the main complication of PVC, avoiding phlebitis is a core challenge for health care professionals and this paper drawn some suggestions to better apply clinical judgement in choosing the right anatomical site in order to decrease phlebitis rate. Some studies reported the association between the anatomical site of cannulation and the risk of phlebitis, however, the results are conflicting depending on the research design, methods, variables considered in the study and studied population. Therefore, with the few available evidence, we cannot recommend the anatomical site of peripheral catheterization with lower risk of phlebitis.

This paper highlights the need for a more comprehensive approach to explore the influence of the anatomical site of PVC on the risk to develop phlebitis in adult hospitalized patients. Further original research, with large sample sizes and experimental designs are needed to better address these recommendations. Understanding the risk of phlebitis associated with the anatomical site of cannu-

lation may help to produce knowledge and evidences to support the nursing decision in clinical practice, minimizing the risk for developing complication during peripheral intravenous therapy (Johann et al., 2016).

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