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Effectiveness of topical interventions to prevent or treat phlebitis-related to intravenous therapy: a systematic review and meta-analysis

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UNIVERSIDADE DE BRASÍLIA
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Dissertação apresentada como requisito parcial para a obtenção do Título de Mestre em Ciências da Saúde pelo Programa de Pós-Graduação em Ciências da Saúde da Universidade de Brasília.
Orientadora: Paula Elaine Diniz dos Reis

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“Gosto de ser gente porque, inacabado, sei que sou um ser condicionado mas, consciente do inacabamento, sei que posso ir mais além dele. Esta é a diferença profunda entre o ser condicionado e o ser determinado.”

Paulo Freire

RESUMO

A flebite é uma reação inflamatória grave que pode ser causada pela terapia intravenosa de drogas hiperosmolares. Embora uma variedade de intervenções seja realizada em vários países diferentes, ainda não se sabe quais são os métodos mais eficientes. Este estudo tem como objetivo descrever a eficácia de intervenções tópicas na prevenção ou tratamento de flebites relacionadas à terapia intravenosa. Seguindo os Itens do Checklistpara Revisões Sistemáticas e Metanálises (PRISMA), desenvolveu-se umarevisão sistemática, cuja busca foi realizadaem sete bases eletrônicasde dados: Cinahl, Cochrane, Lilacs, Livivo, PubMed, Scopus e Web of Science. Utilizou-se uma estratégia de busca individual adaptada a cada base, e pesquisa bibliográfica adicional no Google Scholar, e na base Dissertação e Teses da ProQuest. Ensaios clínicos randomizados publicados entre 1998 e 2019 foram considerados, em que avaliasse qualquer intervenção tópica para prevenir ou tratar flebite relacionada à terapia intravenosa. Treze estudosavaliaram a eficácia de intervenções tópicas, como antiinflamatórios não esteroidais (AINEs), óleo de sésamo indicum, formulações de heparina sódica, chá e pomada de *Chamomilla recutita* e de *Rosmarinus officinalis*. Ao todo, 2.015 pacientes foram recrutados durante a hospitalização com diferentes tipos de terapias intravenosas, como reposição de fluidos, antibióticos, quimioterapia e infusão de antiarrítmicos. Todos os estudos usaram escalas visuais para classificar flebite de acordo com sinais e sintomas no local do cateter. No entanto, um alto nível de heterogeneidade entre os estudos dificultou uma análise quantitativa para estabelecer a melhor intervenção. Como parte importante da rotina de enfermagem, as complicações relacionadas à terapia intravenosa são foco constante de novos estudos, e novas evidências são constantemente descobertas para melhorar o processo de hospitalização dos pacientes, bem como seu bem-estar.

Palavras-chave: Flebite, periflebite, infusão intravenosa, revisão sistemática.

ABSTRACT

Phlebitis is a severe inflammatory reaction that can be caused by the intravenous therapy of hyperosmolar drugs. Although a variety of interventions are performed in several different countries, it is yet unknown what are the most efficient methods. This study aims to describe the effectiveness of topical interventions on the prevention or treatment of phlebitis-related to intravenous therapy. Following the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA), a systematic review was developed, in seven different databases: Cinahl, Cochrane, Lilacs, Livivo, PubMed, Scopus, and Web of Science. An individual search strategy adapted for each one was used, and additional gray literature search was performed on Google Scholar, and ProQuest Dissertation & Theses. Randomized controlled trials (RCTs)published between 1998 and 2019 were considered, in which any topical intervention was applied to prevent or treat phlebitis-related to intravenous therapy. This review evaluates 13 RCTs and compares the effectiveness of topical interventions, such as the application of non-steroidal anti-inflammatory drugs (NSAIDs), *Sesame indicum* oil, heparin sodium formulations, *Chamomilla recutita* tea and ointment, and *Rosmarinus officinalis* ointment. A total of 2,015 patients were recruited during hospitalization treatment with different types of intravenous therapies, such as fluid replacement, antibiotics, chemotherapy, and antiarrhythmic drugs. All studies used visual scales for grading phlebitis according to signs and symptoms on the catheter site. However, a high level of heterogeneity between studies hindered a quantitative analysis to stablish the best intervention. As an important part of nursing routine, complications related to intravenous therapy are constant focus of new studies, and new evidences are constantly being discovered to improve the hospitalization process of patients as well as their wellbeing.

Key words: Phlebitis; periphlebitis; Drug therapy; therapeutics; Peripheral Vascular Diseases; systematic review; topic interventions.

FIGURES LIST

TABLES LIST

ABBREVIATIONS LIST

PIVC – Peripheral Intravenous Catheter

PIT – Phlebitis-related to intravenous therapy

NSAIDs – Non-steroidal anti-inflammatory drugs

RCTs – Randomized Controlled Trials

SUMMARY

INTRODUCTION

Phlebitis is an inflammatory reaction of the venous tract and surrounding tissues that can be related to mechanical, chemical or microorganism's infections factors [1]. It is a common complication of intravenous therapy, considering 33%-67% of patients are submitted to intravenous puncture and have a peripheral intravenous catheter (PIVC) inserted during their hospitalization [2,3]. Recent data shows that approximately 330 million short PIVCs are sold annually in the USA, and over a billion PIVCs are inserted each year in hospitalized patients worldwide [3].

The inflammatory process begins with the disturbance of the vein endothelium, which is firstly caused by the friction oh the vascular apparatus against the vascular endothelium. Next, the hyperosmolarity of the administered solution, or microorganisms and toxins act on said endothelium, triggering the release of serotonin, bradykinin, and histamine, which are inflammatory agents that can cause vasodilatation. This process increases vascular permeability and will promote the extravasation of proteins and blood plasma toward the interstitial space, causing and edema and pain [4].

Histamine increases the platelet aggregation and soon there is a thrombotic formation along the vein wall that extends all the way to the lumen of the vascular apparatus, characterized by localized erythema and a palpable vascular cord of up to 3.5 cm. Leukocytes begin to migrate to the site where the inflammation has taken hold, augmenting the local edema.

The vascular cord, which was palpable earlier, now becomes visible (7.5-15 cm), and localized heat becomes perceptible upon palpation. Exudates can be present at the site of the vein puncture. Pyrogens, resulting from leukocytary

apoptosis, now stimulate the hypothalamus to increase the body temperature. In this phase, phlebitis is characterized by a vascular strain that is palpable to the extent of more than 15 cm along the vascular passage, is enriched, thick, and sensitive, and shows classic signs of inflammation: pain, heat, erythema, and edema [4].

Phlebitis can be a consequence of the infusion of irritant and vesicant drugs, mechanical friction or microorganisms, when related to intravenous therapy (IT), as illustrated on Figure 1 [5].

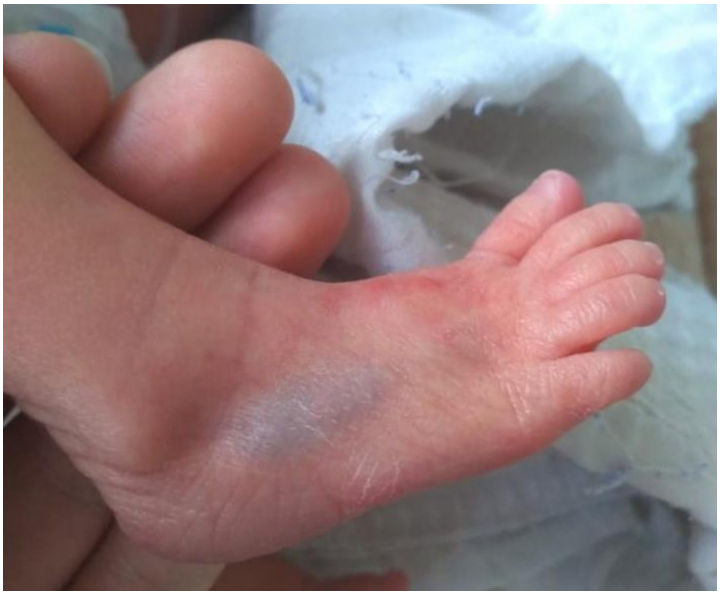


Figure 1. Chemical phlebitis caused by the intravenous infusion of parenteral nutrition. Authorized photograph from the personal collection of the author, 2019.

The diagnosis of phlebitis is made through signs and symptoms of local pain, tenderness, swelling, induration and erythema of the venous tract, and a palpable cord-like vein on the infusion site, requiring immediate interruption of the infusion and removal of vascular access device [6]. Sings of induration, tenderness and swelling are visible on Figure 2. Phlebitis may permanently compromise the endothelium of the vein, reducing the possibilities of any future IT to be placed on the damaged

vein[7]. Patients diagnosed with phlebitis on the first placed catheter were 5.1 times more likely to develop post infusion phlebitis on subsequent catheterizations [1].

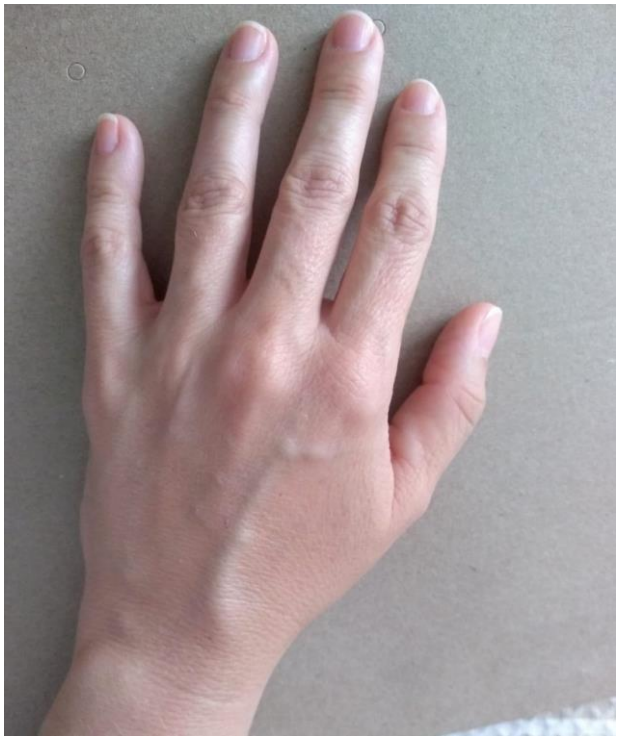


Figure 2. Post infusion phlebitis. Authorized photograph from the personal collection of the author, 2019.

FACTORS INVOLVED IN THE DEVELOPMENT OF PHLEBITIS

Many factors are involved in the development of phlebitis, as the procedure of peripheral catheterization is invasive, there is a need for greater consistency in the choice, insertion and management of short PIVCs. This is particularly relevant in oncology, with the growing trend for patients to receive many different courses of IV treatment over a several years, sometimes with only short remissions. Bertoglio et al [(3)] reviewed the best practices for the insertion of PIVC, being the most relevant:

Vein status

Prior to PIVC insertion, it is important that an appropriate insertion site has been selected (the forearm is preferred, avoiding joints). The chosen vein for insertion should be inspected and carefully palpated. Potential aids for improving venous access success should be considered, such as vein visualization tools (near-infrared light or ultrasound, as available).

Size and nature of catheter

A PIVC of appropriate size (gauge and length) should be selected depending on the patient's veins: the diameter (gauge) is important for patients with very thin veins, while the length is important for obese patients with deeper veins. PIVCs ranging in size from 20 to 24 G are strongly recommended even for adult patients [(3)]. In addition, particular consideration should be given to the vein/catheter ratio, as previously assessed for peripherally inserted central catheters [(3)].

Duration of infusion

The use of prolonged infusions is specifically discouraged for vesicant and hyperosmolar infusates. The use of infusion pumps, requires the use of a newly inserted cannula and blood flow should be routinely checked during infusion [3].

Acidity and osmolality

The acidity and hyperosmolality of parental nutrition solutions offer a great risk for phlebitis, first described by Kuwajara et al in 1998 [8].The main reason why IT can cause an inflammation of the vein is due to hyperosmolar fluids, with osmolarity rate greater than 600 mOsm per liter, and solutions or medications with a pH less than 5 and greater than 9 [1].

Medications can be classified as irritants, vesicants or both, varying according to venous tissue damage and severity of the symptoms. Therefore, patients experiencing specific intravenous therapies such as chemotherapy or arrhythmia reversion treatment are more susceptible to chemical phlebitis due to the high toxicity of the drugs to vascular endothelium, such the case of antineoplastic agents, and low pH level of 3.8 - 4.0 of the antiarrhythmic agents [9,10].

The movement of particles through the cell membrane occurs through four transport mechanisms: passive transport, which consists of diffusion, osmosis, and filtration; and active transport. Substances are transported between the intracellular and the extracellular compartment by these four mechanisms.

It is important to establish that osmosis is the passage of water from an area of lower concentration of particles to one with a higher concentration of particles through a semi permeable membrane. This process tends to equalize the concentration of two solutions, and is known to govern the movement of body fluids between the intracellular and extracellular compartments, therefore influencing the volumes of fluid within each. Through the process of osmosis, water flows through semi permeable membranes toward the side with the higher concentration of particles[1].

When cells are placed in a hypotonic solution, which has a lower effective osmolarity than intracellular fluids, they swell as water moves into the cells. When they are placed in a hypertonic solution, which has a greater effective osmolarity than intracellular fluids, they shrink as water is pushed out of the cells[1].

Solutions that have an osmolarity of 250 to 375 mOsm/L are considered isotonic solutions. They have no effect on the volume of fluid within the cell; the solution remains within the extracellular space. Isotonic solutions are used to expand the extracellular fluids compartment. Hypotonic solutions have less salt in their composition than the intracellular space. An osmolarity below 250 mOsm/L will cause water to move into the cell, causing the cell to swell and possibly burst. By lowering the serum osmolarity, body fluids shift out of the blood vessels into the interstitial tissue and cells[1].

TYPES OF PHLEBITIS

Phlebitis can be classified accordingly its cause in chemical, mechanical, bacterial and post-infusion phlebitis[11]. The definition of each type is described on Figure 3.

Types of phlebitis	Definition
Chemical	Occurs when the infusion of drugs that alter the osmolarity of the solution and lead to irritation of the intima tunica, the inner layer of the vein, as well as dosage, concentration and time of infusion[1].
Mechanical	Caused by the device used on the peripheral access, either by displacement inside the vessel (traction, rotation), by multiple attempts of puncture or even by incompatibility of the gauge with the caliber of the vein [11].
Bacterial or caused by particle agents	Vascular inflammation caused by bacterial infection, as a consequence of inadequate asepsis in skin, inadequate preparation or attachment of the device, which allows the entry of microorganisms [11].
Post-infusion phlebitis	Vascular inflammation occurred within 24 or 48 hours after termination of infusion and withdrawal of the device[11].

Figure 3 – Different types of phlebitis.

CLASSIFICATION OF PHLEBITIS

There are currently 71 scales found to evaluate and classify the signs and symptoms of phlebitis. According to a systematic review of such scales by Ray Barruel et al [12], it is still impossible to determinate the most efficient scale since they

have not been validated[11]. The most used scale is the Visual Infusion Phlebitis Scale published by Infusion Nurses Society (INS)[13].

In general, phlebitis is classified as 0 to 4 degrees, being:

- 0 - absence of clinical signs;
- 1 - erythema at the site of venous access with or without pain;
- 2 - erythema, edema and pain at the venous access site;
- 3 - visible cord formation along the venous path and palpable venous cord;
- 4 - palpable venous cord, pain at the access site with erythema, drainage of purulent exudate.

It may progress to phlebosclerosis, which is venous stiffening resulting from endothelial thickening, which occurs because of phlebitis and prolonged infusion of intravenous vesicant and irritant medications.

It is important to emphasize that the clinical manifestations of phlebitis can occur not only during the stay of the vascular device, but also after its withdrawal. In a study developed by Urbanetto, Peixoto and May (2017) a significant rate of phlebitis occurred after the device was withdrawn, reiterating the need for monitoring and recording of vascular access evaluation constantly, not only during the period in which the patient receives the prescribed antineoplastic or supportive medication [14]. Maintaining a fixation or stabilization that promotes adequate visualization and monitoring of the puncture site is equally important[14].

Nowadays, there is a need of protocols to help health care professionals in the prevention and treatment of chemical phlebitis, especially when it is related to therapies on the venous site. There is a systematic review about pharmacological treatments to phlebitis, including a range of creams and gels with heparinoids in the formula, such as a 5-mg glyceryl trinitrate patch with cream of heparin, glyceryl trinitrate in gel form with heparinoid substances, piroxicam in gel form with polysulfate of mucopolysaccharide (Piroxicam), and a nonsteroidal anti-inflammatory drug diclofenac sodium in gel form or oral form, and also a notoginseny cream tested in China [4]. A recent review of 11 studies evaluated the effects of topical interventions to treat post infusion phlebitis, including other systematic reviews among randomized controlled trials (RCTs) [15]. However, the published reviews did not present a quantitative analysis or the perspective of prevention either [4,15].

The importance of focusing on topical interventions when treating phlebitis is to provide more independence for the patient, allowing him to easily continue the treatment at home, being not necessarily the intake of another medication by oral or intravenous route. Considering that most antineoplastic agents are metabolized in the liver, for example, choosing a local treatment rather than a systemic anti-inflammatory medication will not increase hepatic toxicity and organ overload [16].

Considering that phlebitis is an important issue to nursing, we developed a systematic review with the follow question: “What is the effectiveness of topical interventions to prevent or treat phlebitis caused by intravenous infusion?”.

OBJECTIVES

Primary objective

In this systematic review, the main objective was to identify topical interventions applied to prevent or treat phlebitis-related to intravenous therapy, and to evaluate the effectiveness of such interventions.

Secondary objectives

- To identify the incidence of phlebitis-related to intravenous therapy on patients under intravenous infusion;
- To identify the types and the frequencies of solutions in which phlebitis is more common;
- To identify the severity of the phlebitis accordingly the topical interventions applied to prevent or treat phlebitis;
- To evaluate the effect of the topical interventions to delay the occurrence of phlebitis.

METHODS

Protocol and registration

This systematic review was carried according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA [17] Checklist which can be found on Appendix 1. The review protocol was registered at the International Prospective Register of Systematic Reviews – PROSPERO [18], number CRD42018083553.

Eligibility criteria

RCTs published between 1998 and 2019 were considered, in which the objective was to investigate the effects of the use of any topical interventions in the prevention or treatment of PIT. Since the need to collect current data due to the thematic of this review that is constantly being updated, this time frame was stablished.

Studies were excluded for the following reasons: 1) full text not found, 2) sample included subjects under 18 years old, 3) data not individualized for PIT, 4) reviews, letters, conference abstracts, personal opinions, case reports, observational studies or preclinical studies, 5) original article in Chinese or non-latin languages, 6) RCT protocol for unpublished trial, 7) article comparing two different intravenous therapies, and 8) deep vein thrombosis in lower limbs.

Information sources and search strategies

Studies were identified using an individual strategy adapted for each electronic database: CINAHL, Cochrane Controlled Register of Trials (CENTRAL), LILACS, LIVIVO, PubMed, Scopus, and Web of Science. In addition, a grey literature search was performed using Google Scholar and ProQuest Dissertations & Theses Global databases. Additional studies were identified through hand-searching or expert suggestions. Hand-searching were performed in the reference lists of selected articles and were requested expert suggestions, in order to recover potentially relevant studies that could have been missed during the electronic databases searches.

After collecting all references, duplicates were excluded by using appropriate software (EndNoteBasic®, Thomson Reuters, USA). The duplicate references were identified and excluded in this software and posteriorly any additional duplicate not identified by EndNote, was found and excluded using Rayyan qcri, a free software to manage references for systematic reviews (Qatar Computing Research Institute, Doha, Qatar). All searches were conducted on February 13th, 2019.

Study selection

Study selection was conducted by two investigators (CBG and CSC) in two phases. In phase 1, each one, independently, screened the titles and abstracts of potentially relevant studies and selected articles that appeared to meet the inclusion criteria based on their abstracts. In phase 2, the same reviewers independently read

the full-text of all selected articles and excluded studies that did not meet the inclusion criteria. Any disagreements, either in the first or second phases, were resolved by discussion and agreement between the two reviewers. If a consensus could not be reached, a third author (PEDR) was involved to make a final decision.

Data collection process and items

The first reviewer collected the required information from the selected studies and the second reviewer crosschecked all the retrieved information for accuracy. Data collection included study characteristics (author(s), year of publication, country, objective), population characteristics (sample size, age, population setting, type of intravenous solution), intervention characteristics (intervention, control, frequency of intervention, follow-up period, phlebitis criteria), and outcome characteristics (main results). If the required data were not complete, attempts were made to contact the authors to retrieve any pertinent missing information.

Risk of bias and quality assessment in individual studies

The risk of bias of each study included was evaluated individually using the Cochrane Risk of Bias Tool [19] and classified as low, high or unclear. Evaluation of RCTs included allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Two investigators performed this process (CBG and EBF) and disagreements between the two reviewers were resolved by a third investigator (PEDR).

Summary measures

The primary outcome for prevention studies was the development of phlebitis and for treatment studies, the regression of symptoms, reported according visual phlebitis scales. Additional measurements considered in this review were risk ratio (RR) and incidence when interventions were comparable.

Synthesis of results

A descriptive synthesis was performed of all included studies for data combination. Meta-analysis was planned whenever RCTs were considered relatively comparable and homogenous according to study design, intervention and outcomes. Heterogeneity among studies was evaluated considering clinical or methodological characteristics and calculated by inconsistency indexes (I^2).

RESULTS

Study selection

During phase 1 a total of 2,453 references were found across seven databases searched and imported for duplicates removal. Two articles were identified through hand search and expert indication. After duplicates were removed, the screening of 1,613 studies proceeded, in which 41 remained for full text reading (phase 2). Twenty-eight studies were excluded after full-text assessment and the reasons for their exclusion are listed in Appendix 2. A total of 13 randomized control trials were included in this review, being 7 of them for preventing PIT, and 6 for treating it. A flow chart detailing the process of identification, screening, eligibility and inclusion of the studies is shown in Figure 4.

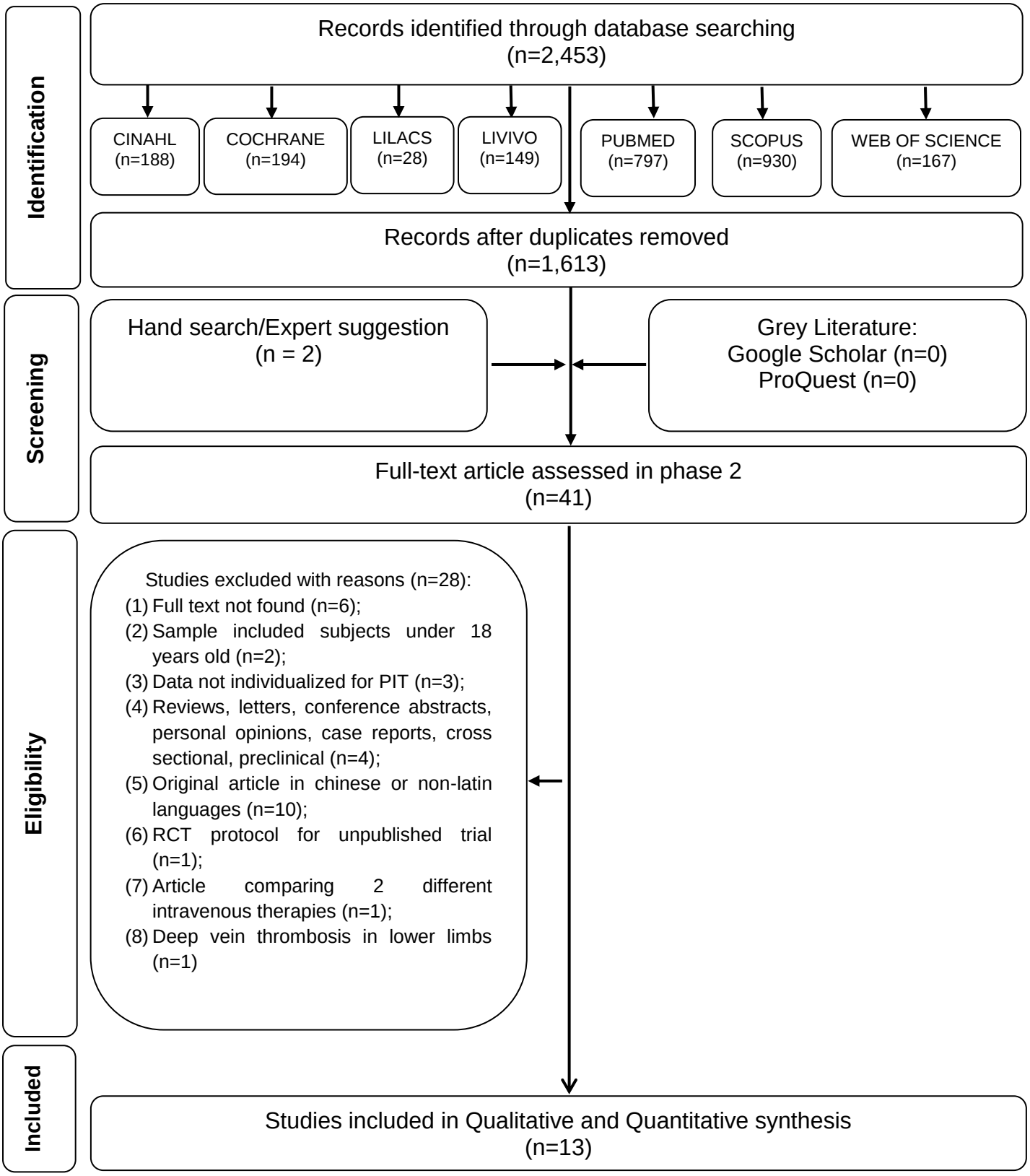


Figure 4. Flow chart adapted from PRISMA.

Characteristics of studies

The studies included were published from 1999 to 2019, in English and Spanish. Five studies were from Iran [20–24], two from Spain [25,26], two from India [27,28], one from Turkey [29], Brazil [7], Argentina [30], and Singapore [31]. A total of 2,015 patients were recruited during hospitalization treatment with different types of intravenous infusions, such as fluid replacement, antibiotics, chemotherapy, and antiarrhythmic drugs.

The interventions to prevent PIT approached in seven studies consisted on a glyceryl trinitrate patch [29], sesame oil [21,32], rosemary ointment [23], chamomile ointment [20], heparin sodium solution and gel [28], and 2% chlorhexidine in 70% alcohol swabs for antisepsis combined with a spray film dressing on catheter site [33], 2018). Meanwhile, interventions found for treatment included magnesium sulfate dressing [27], glyceryl trinitrate patch [26], heparin gel [25], diclofenac gel [30], sesame oil [24], and warm compress with chamomile tea [34]. A summary of the descriptive analysis of studies can be found on Table 1.

Regarding the evaluation of PIT, all studies used visual scales for grading phlebitis according to signs and symptoms on the catheter site. Eight studies [7,20,21,23,24,27,28,33] applied the Visual Infusion Phlebitis Scale [35], four authors [26,29,30,36] created their own scale specific for the research, and one [37] applied the Royal College of Nursing Phlebitis Scale. One study also evaluated severity of pain using the Visual Analog Scale (VAS), specific for pain assessment [24].

	STUDY CHARACTERISTICS		POPULATION CHARACTERISTICS			INTERVENTION CHARACTERISTICS					OUTCOME CHARACTERISTICS
	Author, Year, Country	**Objective**	**Total *n* (F:M)**	**Age Mean/ range (years)**	**Type of intravenous solution**	**Intervention (n)**	**Control (n)**	**Frequency of intervention**	**Follow-Up**	**Phlebitis Criteria**	**Main Results**
PREVENTION	Çokmez et al, 2003, Turkey	To study the effects of GTN and a NSAID gel in preventing the development of PIT	386 (200:186)	18-82	5% dextrose saline, 5% dextrose in water and 0.9% NaCl	GTN group: a transdermal patch releasing 10 mg/day of GTN was placed on the skin over the course of the cannulated vein (n = 136). NSAID group: a pinch of gel containing an NSAID was applied to the skin over the course of vein (n = 127)	None (n = 123)	Every 24 hours	Up to 72 h after insertion of the cannula	Presence of two or more of the following signs: pain, erythema, swelling, excessive warmth, and/or a palpable venous cord.	NSAID and GTN groups presented better results (P < 0.05). Number of phlebitis (72h): Control group: 34.9% (43 out of 123) GTN group: 30.8% (43 out of 136) NSAID group:14.1% (18 out of 127)
	Bagheri-Nesami et al, 2015, Iran	To determine the effect of SO on the prevention of amiodarone-induced PIT	36 (21:15)	Group SO: 68.5 Group Liquid paraffin: 70.27	Amiodarone	Five drops of pure SO were rubbed within a 10 cm radius of the infusion site (n = 18)	Five drops of liquid paraffin were rubbed within a 10 cm radius of the infusion site (n = 18)	4 times in 24 hours	30 h and 10 min (24 h of amiodarone infusion and also 6 h after)	Visual Infusion Phlebitis Scale (VIPS)	SO group presented better results (P <0.001) Number of phlebitis (over 30 h and 10 min after catheterization): SO group: 38.9% (n = 7) CG: 77.8% (n = 14)

PREVENTION	Sheikhi et al, 2018, Iran	To determine the effect of rosemary topical ointment on PIT	46 (16:30)	18-60	Antibiotics	Application of rosemary ointment before venepuncture, with a length of 1.5 cm (n = 23)	Application of Eucerin as a placebo (n = 23)	Twice a day for 3 days	72h	VIPS	There was a significant difference in the ratio of PIT within 48h application of rosemary ointment (0%) and control group (30%), and after 72h (approximately 25% in rosemary group vs. 65% in control group)
	Gunasegaran et al, 2018, Singapore	To evaluate the use of chlorhexidine gluconate and spray-on film dressings on the incidence of SPC related PIT	960	21-99	Unknown	Skin antisepsis with 70% isopropyl alcohol swabs preinsertion (n = 538)	Skin antisepsis with 2% chlorhexidine with 70% isopropyl alcohol swabs preinsertion (n = 422)	One-time preinsertion of catheter	48h	VIPS	There is no difference between interventions (P=0.143) 1% (6 out of 538 patients) developed phlebitis 0.2% (1 out of 422 patients) developed phlebitis. Patients who had catheters in situ for >24 to <48h, 1% (n=2) had phlebitis (VIP score 2 or greater)
	Nekuzad et al, 2012, Iran	To determine the effect of external use of SO in the prevention of PIT	60	30-70	5-Fluorouracil	5 drops of 100% SO, twice a day (n = 30)	None (n = 30)	Twice a day, from the 1st to the 14th day of CHT	14 days, after being released and at their next return to the hospital	Infusion therapy scale standards of the Royal Nursing College	SO group presented better results (P <0.05; RR = 8; ARR = 70%) SO group: 10% (3 out of 30) developed phlebitis grade 1 Control group: 80% (24 out of 30) developed phlebitis grades 1, 2 and 3

PREVENTION	Sharifi-Ardani et al, 2017, Iran	To determine the effect of chamomile ointment on the incidence of PIT due to amiodarone therapy in patients	40 (19:21)	53-57	Amiodarone	Rubbed a pea-sized amount of chamomile ointment (1.5%) up to 10 cm superior to the cannula site (n = 20)	Rubbed a pea-sized amount of ointment of lanoline up to 10 cm superior to the cannula site (n = 20)	Every 8 h for 3 days	3 days	VIPS	Chamomile ointment presented better results (P = 0.023) First Day: 95% (19/20) in the CG had phlebitis vs. 65% (13/20) in the Chamomile group Second Day: 100% (20/20) in the CG had phlebitis vs. 75% (15/20) of Chamomile group. Grades 2 and 3 were lower in Chamomile group
	Saini et al, 2018, India	To compare the incidence and severity of PIT with the application of heparin sodium topical solution (QPS) versus gel formulation heparin sodium (GEL)	74	18-65	Unkown	6–8 drops of topical solution applied on the skin over the cannulated vein around the plaster supporting the IV cannula, in the direction of venous flow (n=41)	1g of topical gel applied on the skin over the cannulated vein around the plaster supporting the IV cannula (n=33)	Every 8 h for 3 days	3 days	VIPS	Absence of PIT was significantly higher (24 patients out of 41) in Group QPS (32.4%) as compared to Group GEL (7 patients out of 33) (9.4%) (*P* = 0.0019); Group QPS: 17 out of 33 patients had PIT; Group GEL: 26 out of 33 patients developed PIT
TREATMENT	Ravindra and Krupa, 2015, India	To determine the effectiveness of glycerin magnesium sulphate dressing on PIT	60	>14	Any intravenous infusion	20 g of magnesium sulphate diluted in 100 mL of glycerin and this combination applied on site of phlebitis with help of roller bandage and the limb will be elevated (n = 30)	Applying a warm, moist compress to the affected site (n = 30)	Twice a day for 2 days	2 days	Jackson's visual infusion phlebitis scale	Dressing group had better results (p < 0.001) GMS dressing: mean score 1.10 (SD 0.71) CG: mean score 2.53, (SD 0.78). GMS dressing group had scores 1 (50%) and 2 (30%), CG group scores 1 (10%), 2 (33.3%), 3 (50%), 4 (6.7%)

TREATMENT	Reis et al, 2011, Brazil	To analyze and compare the therapeutic efficacy of different dosages of chamomile infusion tea in cancer patients with PIT	25 (13:12)	20-30	IDA + ARA-C	20 cm² cotton compresses moistened with the chamomile infusion tea at dosages 1.25% (n = 5), 2.5% (n = 5), 5% (n = 5) and 10% (n = 5) at 38 °C	Lukewarm water at 38 °C (n = 5)	Three times a day, for 20 minutes	2 days after regression of symptoms	VIPS	Time of regression of Ph was shorter for groups with 2.5% concentration and 5% concentration. Groups vs. control mean of regression time: 1.25%: 57.8h (P < 0.001) 2.5%: 29.2h (P < 0.001) 5%: 38.8h (P < 0.001) 10%: 49.4h CG: 110.4h
	Bigdeli Shamloo et al, 2019, Iran	To evaluate the effects of topical application of SO on the pain severity of PIT	60 (33:27)	20-60	FOLFOX-4 protocol	10 drops of SO (about 3 mL) applied to the phlebitis site using a dropper and massage for 5 minutes in a 10 cm radius of the phlebitis in circular movements	Massage for 5 minutes in a 10 cm radius of the phlebitis in circular movements without any topical extract	Twice a day, every 12 hours, for seven consecutive days	7 days	VIPS	Decrease in the pain severity during the seven days (F=720.66, Ptime < 0.001) considering gender as a covariate. Mean changes of the pain severity on experimental vs. control: Third day: (−2.30 ± 0.16 vs. −1.60 ± 0.19, P=0.009) Fifth day: (−4.70 ± 0.16 vs. −2.80 ± 0.25, P < 0.001) Seventh day: (−6.80 ± 0.24 vs. −3.76 ± 0.31, P < 0.001)
	Ruiz Trillo et al, 2006, Spain	To evaluate the application of nitroglycerine as an alternate treatment to heparinized cream to alleviate symptoms of PIT	22 (15:7)	18-88	Antibiotics and fluid replacement therapy	Transdermal patch of nitroglycerine 5 mg (n = 11)	Heparinoid ointment (n = 11)	Not reported.	3 days	0 – none; 1 – local pain; 2 – pain and erythema or possible inflammation; 3 – all the signs in 2 + palpable cord less than 7 cm; 4 – all the signs in 3 + palpable cord more than 7 cm; 5	NTG group had better results. 3rd day: phlebitis had disappeared in 9 out of 11 patients of NTG group, while only 2 patients had an improvement of symptoms on the control group.

										- thrombosis	
TREATMENT	Becherucci et al, 2000, Argentina	To study the effectiveness and safety of the topical and oral administration of diclofenac in the treatment of PIT	120 (50:70)	-	Unknown.	Topic Diclofenac 1% emulsion gel applied to the site of phlebitis each 8 h during 48 h (n = 40)	No intervention was applied (n = 40)	Every 8 hours for 48 hours	48 h after signs and symptoms of PIT	Erythema and Edema: levels 2, 4, 6, 8 and 10 according to the area size Heat: levels 2, 4, 6, 8 and 10 measured by a thermometer Pain: visual scale from 1 to 10	Diclofenac gel group presented less scores of erythema, edema, heat and pain. 60% (24/40 patients) presented phlebitis regression vs. 20% (8/40) of CG
	Vilardell et al, 1999, Spain	To assess the clinical efficacy of a topical gel of heparin, applied to patients with PIT secondary to indwelling intravenous catheter	126 (50:76)	>20	Infusion solution 5% Dextrose (n=49); 0.9% Saline (n=48); Glucosaline (n=21); Other (n=8)	Topical sodium bovine heparin as a 1000 $IU.g^{-1}$ gel preparation containing 60 g of gel each, in an amount sufficient to cover the surface of the phlebitis lesion (n = 61)	Placebo excipient provided in tubes containing 60 g of gel each (n = 65)	3 times a day (morning, noon and evening)	Treatment continued until clinical healing or for a maximum of 7 days	Light (venous induration, redness or local temperature increase), Moderate (mentioned signs + tenderness), Severe (mentioned signs + spontaneous pain), or “absent"	Heparin group had better results (P = 0.033; RR = 1.69). Healing of phlebitis was achieved in 27 patients (44.3%) in the intervention group, compared with 17 patients (26.1%) in the control group. Heparin group: 1/59 developed severe phlebitis; 6/62 in the CG by the end of the follow-up

Abbreviation: GTN = transdermal glyceryl trinitrate; IDA + ARA-C = idarubicin and cytarabine; INS = Infusion Nursing Society; NSAID = topical non-steroidal anti-inflammatory drug; Ph = phlebitis; PIT = phlebitis-related to infusion therapy; RCT = randomized clinical trial; SO = sesame oil; SPC = short peripheral catheter; TFSI = Superficial thrombophlebitis induced by intravenous infusion; FOLFOX-4 protocol = the first day: oxaliplatin 80 mg/m2 + leucovorin 200 mg/ m2 + 5-fluorouracil 400 mg/m2 bolus and 600 mg/m2 infusion, and the second day: leucovorin 200 mg/m2 + 5-fluorouracil 100 mg/m2 infusion.

Risk of bias within studies

As only RCTs were included in this review, risk of bias was considered unclear/uncertain when the randomization process was not clearly described in the text. The same applied to blinding characteristics, enrollment of subjects and level of comparability between groups. Five studies presented a low risk of bias [20,21,24,25,33]. Two studies assessed as a moderate risk [7,23], and six studies were assessed as a high risk [26–30,32].

The blinding of outcome assessment had a high risk of bias in almost half of the analyzed references [7,23,26,29,30] and unclear in three articles [27,28,32], being the category with higher risk of bias due to the nature of the interventions. Since the variety of different formulas of the interventions between the groups of each study, there was also a high risk in blinding of participants and allocation concealment [7,26,28–30]. An unclear risk was detected in allocation concealment [21,23,27,33] and random sequence allocation [23,26–28,30,32] due to the lack of information on how it had been done by the researchers. Most studies presented an unclear risk of other bias [23,26–30,34,37]. The risk of bias assessment was reported on Figure 5.

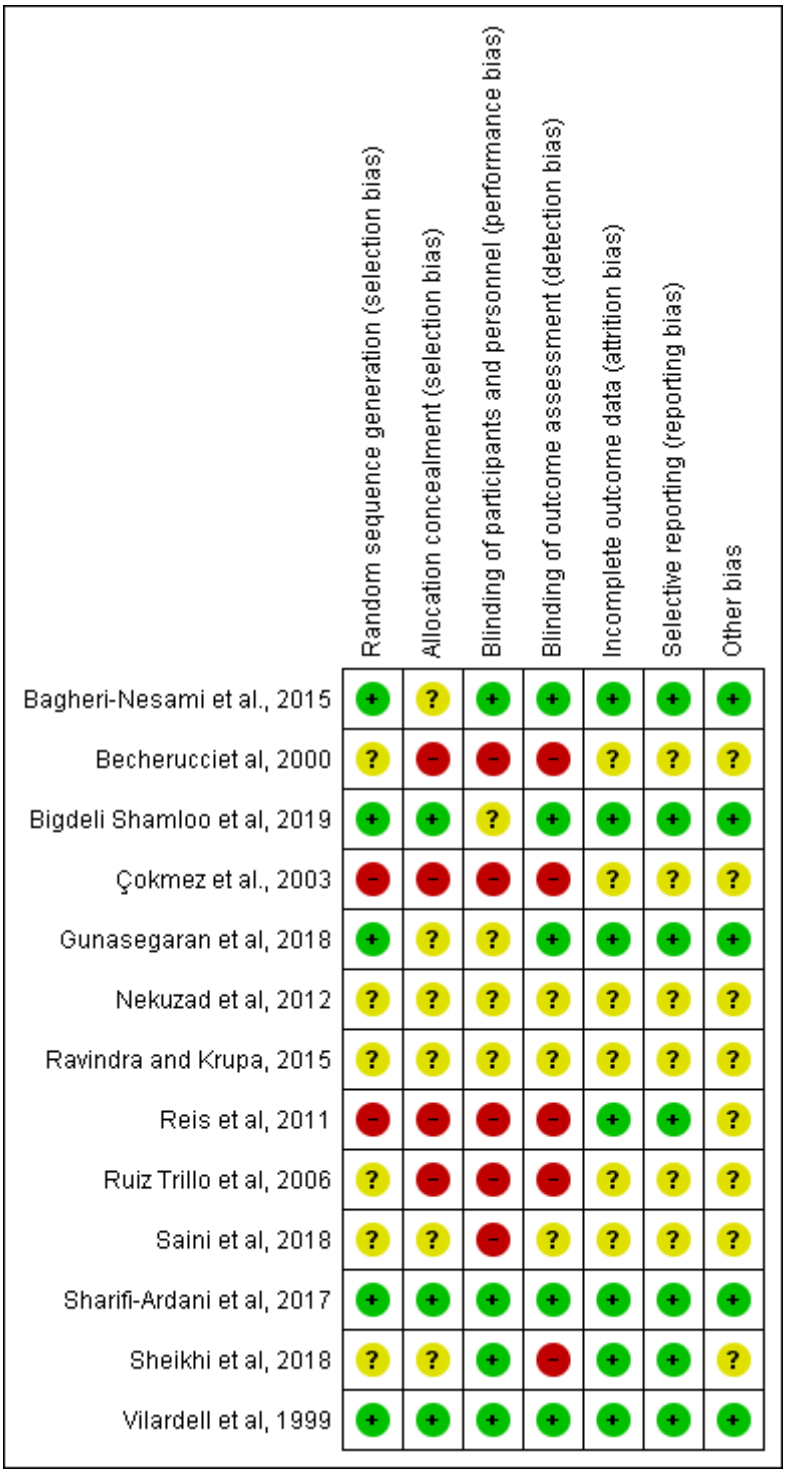


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Results of individual studies

The topical interventions to prevent or treat PIT were various and reported the primary outcomes according to the type of intervention.

Once the intention with these interventions was to prevent the outcome from happening, studies compared the incidence of PIT between the studied groups. Six of 7 studies included in this review reported a smaller occurrence of PIT within the experimental groups [20,21,23,28,29,32]. The interventions which presented better results when compared with controls were sesame oil with occurrences varying from 10% (3/30) vs. controls (80%, 24/30) [32] and 38.9% (7/18) vs. controls (77.8%, 14/18) [38], heparin sodium solution 42% (17/41) vs. controls (78%, 26/33) [28], non-steroidal anti-inflammatory drug gel with 14.1% (18/127) vs. controls (34.9%, 43/123) [29], rosemary ointment with 25% (6/23) vs. controls (65%, 15/23) [23], and chamomile ointment with 75% (15/20) vs. controls (100%, 20/20) [20].

Sesame oil (SO) was used in two different studies for prevention of PIT [32,38]. Bagheri-Nesami et al [38] evaluated the effect of SO on the prevention of amiodarone induced PIT with a sample of 36 patients undergoing peripheral intravenous treatment. The most frequent diagnosis was atrial fibrillation (n=25) and catheterization was performed in patients' left hand in 83.3% (n=15) of the SO group and 77.8% (n=14) of the liquid paraffins group. Findings describe better results for SO group versus liquid paraffin ($P<0.001$).

Although the intervention was also SO to prevent PIT in Nekuzad et al. [37] study, this sample of 60 patients only included patients undergoing intravenous chemotherapy treatment, specifically with 5-Fluorouracil. The relative risk of phlebitis was 8 times higher in the control group (n=30) than the

intervention group (n=30), once incidence of PIT was 70% higher in the control group (P<0.05).

When comparing three different groups, one using transdermal glyceryl trinitrate patch (n=136) versus non-steroidal anti-inflammatory drug gel (n=127) and no intervention for the control group (n=123), Çokmez et al. [29] described a higher incidence of PIT on versus non-steroidal anti-inflammatory drug gel and on the control group. The infusion site most assessed was the forearm (n=246), but also dorsum of the hand (n=81) and cubital fossa (n=17). By the end of the 72 hours follow-up period, 34,9% (n=43) of patients on the control group had PIT and 30.8% (n=43) of the glyceryl trinitrate patch group versus 14.1% (n=18) of the versus non-steroidal anti-inflammatory drug group.

The other pharmacological intervention to prevent PIT was the anticoagulant heparin sodium in two different formulations. Saini et al. [28] recruited 74 patients and compared the efficacy of a quick penetrating solution of heparin (n=41) and heparin sodium gel (n=33). The quick penetrating solution group presented less PIT than the gel group (P=0.0019), as the severity of PIT was also inferior especially for Grade II (group experimental 13.5% vs. group gel 22.9%; P=0.0279).

One study aimed to prevent PIT caused by antibiotics in ICU patients, Sheikhi et al. [23] evaluated a rosemary ointment (n=23) versus an Eucerin ointment as placebo (n=23). The statistic difference is in favor of the intervention group in decreasing the incidence of phlebitis caused by antibiotic therapy, 72 hours after topical application of rosemary ointment.

Chamomile ointment was one of the interventions presented with a positive result when compared to lanoline as a placebo. Sharifi-Ardani et al. [20]

also tested an intervention to prevent PIT in patients undergoing amiodarone intravenous treatment. Reportedly, 95% (n=19/20) of participants in the control group had PIT on the first day of the study and 100% (n=20/20) on the second day. Meanwhile, it occurred in 65% (n=13/20) of patients on the first day and 75% (n=15/20) on the second day in the intervention group (P=0.023).

Among the interventions for prevention, only one study reported there was no difference between the groups evaluated (Gunasegaran et al., 2018). This study tested two different antisepsis before venipuncture and two different dressings to prevent PIT. In one group, antisepsis with 70% isopropyl alcohol swabs and an adhesive bandage for dressing were applied in 538 patients. Patients in the second group (n=422) received 2% chlorhexidine combined with 70% isopropyl alcohol and a film dressing. Only 1% of patients developed phlebitis on the first treatment method and 0.2% on the second treatment method.

Concerning to the treatment, all the studies included in this systematic review shown regression of symptoms of PIT [26,27,34,36,39,40]. Three studies presented better results in the regression of symptoms of PIT when compared between experimental and control groups [26,30,36]. One study with sesame oil (24) observed a reduction on the severity of local pain for patients with PIT on the intervention group (-6.80) vs. control (-3.76). Diclofenac 1% emulsion gel presented 60% (24/40) of regression of symptoms of PIT when compared with control (20%, 8/40) [30], bovine heparin gel 44.3% (27/59) vs. control (26.1%, 17/62) [36], transdermal patch of nytroglicerin 80% (9/11) vs. control (20%, 2/11) [26]. One study measured the regression time according with chamomile tea concentration, in which the best result was 2.5% with symptom regression in

29.2 hours [7]. Another study [27] compared the mean score of symptoms of phlebitis, in which the mean difference was -1.43 (1.10 in the experimental group and 2.53 in the control).

To evaluate the effect of bovine heparin gel, Vilardell et al [36] recruited 126 patients and allocated randomly in two different groups, 61 in the experimental group and 56 in the control. Forty-nine patients left the study before the end of follow-up (24 from experimental group and 25 from control group) mostly due to discharge. Results were statistically significant in favor for the experimental group to the healing of phlebitis (P = 0.033); RR (95% CI) = 1.69 (1.03 - 2.78) when compared to control. There was no difference related to the phlebitis grade (severe, moderate or good) in each group.

The reduction of local pain was the aim of the intervention performed by Bigdeli Shamloo et al. [24], where patients who received 10 drops of SO and a massage for 5 minutes (n=30) reported less pain than patients in the control group (n=30). The difference between experimental and control increased during the third (P=0.009), fifth (P < 0.001), and seventh (P < 0.001) day of treatment.

Among the interventions used to treat PIT, Becherucci et al. [30] (Becherucci et al., 2000) tested topic diclofenac 1% emulsion gel in 40 patients with a successful regression of edema (P = 0.000), heat (P = 0.001), pain (P = 0.000), and erythema (P = 0.000). The proportion of patients with phlebitis regression were 60% (24/40) in the experimental vs. 20% (8/40) in the control. There was a third group under evaluation, however since it was an oral intervention, it was not considered in this systematic review.

A transdermal patch of nitroglycerine 5 mg was compared with a heparinoid ointment in patients undergoing antibiotics and fluid replacement therapy. In this study, Ruiz Trillo & Borrero Esteban [26] reported disappearance of symptoms of phlebitis in 80% (9/11) on the third day of treatment vs. only 20% (2/11) in the control group.

The time of regression of PIT was also measured by Reis et al. [7] in a study that compared the effect of the therapeutic efficacy of four different dosages of chamomile tea compress in cancer patients undergoing chemotherapy. Patients submitted Idarubicin and Cytarabine protocol were allocated in five different groups for dosages 1.25% (n = 5), 2.5% (n = 5), 5% (n = 5), 10% (n = 5), and a control group with warm water compress (n = 5). The groups with chamomile tea in 2.5% and 5% concentration had a shorter mean of regression time, 29.2 hours and 38.8 hours, respectively (P = 0.001).

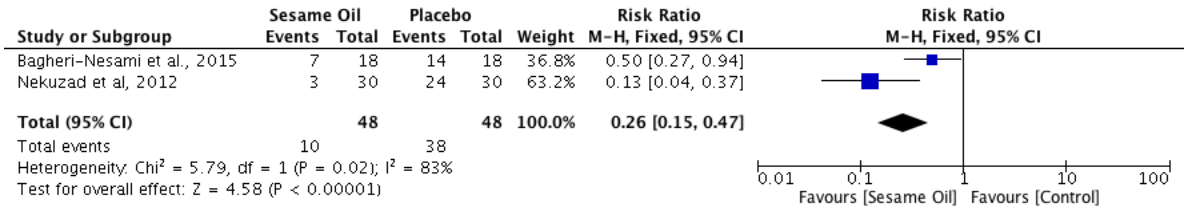
Glycerin magnesium sulphate dressing (20 mg) was applied twice a day in 60 hospitalized patients receiving any intravenous infusion that developed phlebitis [27]. The majority 15 (50%) patients presented medium stage of phlebitis (score 3), 10 (33.3%) had early stage of phlebitis (score 2), and 2 (6.7%) had advanced stage of phlebitis or start of thrombophlebitis (score 4).

Other characteristics and results of the included studies are listed in Table 1.

Synthesis of results

The forest plot (Figure 6) illustrates the results of the meta-analysis and the comparison between the topical intervention (sesame oil) and controls (paraffin) [38], or none [32] groups in the prevention of phlebitis. The Chi^2 results (5,79) and I^2 statistics of 83% indicate heterogeneity between studies. According to these results of a fixed-effect meta-analysis, topical intervention was reported to be more effective than controls for prevention of phlebitis (RR 0,26, 95% CI: 0.15 – 0.47) (Figure 6).

Figure 6. Comparison between sesame oil studies evaluating prevention (n=2).



Risk of bias across studies

The included studies were considered homogeneous regarding the methodology used, considering that all the studies were randomized clinical trials. However, the studies diverged between the population and the interventions evaluated, presenting greater heterogeneity in these aspects. This heterogeneity was evident in the meta-analyses when compared the group that used sesame oil and the control.

DISCUSSION

To the best of our knowledge, this is the first systematic review of clinical trials that evaluated prevention and treatment of phlebitis and presents a quantitative analysis. In this review, we included 13 clinical trials, 7 evaluating prevention [20,23,28,29,32,33,38] and 6 treatment [7,24,26,27,30,36]. Between the studies evaluated, there was heterogeneity concerning the measurement scales of phlebitis, follow-up time and frequency of the application of the interventions.

Short peripheral catheters are largely pointed as the main cause of phlebitis [41] since this procedure occurs in over 80% of hospitalized patients [2]. However, it can be observed that the risk of phlebitis is also related to the type, dosage, and duration of infusion [42]. Meaning that for certain patients, independently of the nursing care with the short peripheral catheters, phlebitis is inevitable due to the irritability of the drugs infused [42]. In such cases, preventing phlebitis can be very effective to lower the incidence of diagnosis or to simply soften the severity of symptoms by using proper treatments [2].

The diagnosis of phlebitis is based on clinical observation of symptoms and signs of inflammation, such as the presence of pain, erythema, edema, local warmth, and tenderness as judged by the professional in charge [13]. Once the signs of phlebitis are identified, assessment scales are used to determine the treatment or the need to remove the short peripheral catheter. There is a gap between the amount of knowledge available and the credibility of that knowledge, for example, there are currently 71 scales to assess phlebitis, but none of them have been validated or established a consensus for the definition of phlebitis [13]. Being so, since the studies use different scales and definitions to

the same problem, it is hard to compare the findings in the literature, which makes it even harder to define efficient parameters to prevent or to treat such condition. In the meanwhile, patients suffer the consequences of poor clinical protocols and multiple catheter replacements that may not be necessary.

Concerning the frequency of the interventions applied, it can be observed that the time variation is attributed to the feasibility to execute the study, and not necessarily to favor the action of the substance under evaluation. The frequency of the application of the sulphate magnesium dressing was twice a day, for two days [27]. Heparin gel was applied three times a day, in the morning, afternoon and evening, for seven days [25], the same frequency was observed in another study, where SO was also applied for 7 days every 12 hours [24]. Warm compress moistened with chamomile tea was applied three times a day for twenty-minutes and continued until symptoms had disappeared for at least 48 hours [7] Topic diclofenac was applied every eight hours for two days [30]. The study with a transdermal patch of nitroglycerine did not report this data [26].

Follow up period could range from a day to two weeks, varying according to the time of insertion of the cannula or regression of symptoms in some of the included studies. The shortest follow up period was of 30 hours e 6 minutes [38] while the longest period lasted 14 days after patients were discharged [32], both in studies approached prevention. In general, other studies accompanied patients for 48 hours after infusion began (Ravindra & Patel, 2015; Gunasegaran et al., 2018), and six studies for 72 hours (Çokmez et al., 2003; Saini et al., 2018; Sheikhi et al., 2018; Sharifi-Ardani, 2017, Ruiz Trillo & Borrero Esteban, 2006). Besides these, there were two treatment studies that followed patients for 48 hours after the regression of symptoms (Reis et al.,

2011; Becherucci et al., 2000) and two others that had follow-up up to 7 days (Villardell et al., 1999; Bigdeli Shamloo et al., 2019).

When it comes to the type of infusion, there was a high incidence of PIT, independently of the type of drug administrated (chemotherapy or amiodarone) in patients on the controls, which supports the strong relationship of irritant substances and occurrence of PIT, despite the mechanical factor of the SPC. In one of the studies, PIT was developed in 24 hours in 95% of the patients in the control [20]. Among studies that patients received chemotherapy, the drugs used were fluorouracil, oxaplatin, leucovorin, idarubicin and cytarabine, all classified as irritants (43), as well as amiodarone. These drugs have lower pH and high osmolarity, leading to tissue damage of the tunica intima of the vein [41]. On the other hand, mechanical phlebitis is related to the trauma caused by the insertion of the canula and can be reported up to 72 hours after cannula placement (44).

To prevent PIT, the most efficient intervention was the non-steroidal anti-inflammatory gel, followed by the application of sesame oil. The mechanisms of non-steroidal anti-inflammatory gel is already known, it is responsible for the inhibition of prostaglandin G/H synthase, or cyclooxygenase, which is the enzyme catalyzing the transformation of arachidonic acid to prostaglandins and thromboxanes responsible for the inflammatory response (45).On the other hand, besides the anti-inflammatory properties, sesame oil has anti-mutagenic, anti-oxidant, anti-cardio, and anti-pyretic protective effects as well as anti-nociceptive property, widely used in Iranian and Taiwanese traditional medicine (39).

When comparing pharmacological treatments to phytotherapy, it is important to remember that the mechanism of action of pharmaceutical

products has been more studied and tested, proving their efficacy. Meanwhile, herbal and natural treatments origin from empirical knowledge, and now is incorporating the evidence-based science. The spread usage of phytotherapy, and its application in clinical studies will provide enough data to define better comparison standards.

Only two studies (Nekuzad et al., 2012, Bagheri-Nesami et al., 2015) were comparable concerning the type of intervention applied for metanalysis. Although both studies used 5 drops of SO to prevent PIT, there were significant differences such as the type of infusion patients were submitted to, sample size, measurement scale and frequency of the intervention. These methodological divergences contribute to a high heterogeneity, complicating the interpretation of the results obtained.

The discrepancy between studies was also an issue when evaluating the level of evidence found in this review. In total, over ten distinct products were used as interventions, varying according to pharmaceutical preparations, main substrate, and pharmaceutical or phytotherapic origins. Such differences affect how the evidence is analyzed and interpreted, leading to a misunderstanding that the results are not reliable, when, in fact, there is not enough data about the effect of each intervention in each population to build a solid conclusion.

CONCLUSION

In conclusion, this study suggests that there is no strong evidence indicating a specific intervention to prevent or treat PIT, with the exception of the sesame oil that presented in the meta-analysis a statistically significant difference when compared to controls for the prevention of PIT. Further studies using larger, well-characterized homogenous groups are needed to further replicate these findings.

Relevance to Clinical Practice

Intravenous catheterization is the most common procedure during hospitalization, performed and supervised by nurses. A variety of interventions are used worldwide as a routine to prevent or to treat the complications of intravenous therapy, such as phlebitis, the focus of this study. It is important to observe that although chemical phlebitis is not as preventable as one caused by microorganisms, there are still measures that can be applied to relieve the signs and symptoms. It is crucial for clinical practice for professionals to know – not only the effectiveness of these interventions – but also to investigate applicability, costs, availability, and all available evidence to determine the best possible practice.

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Appendix 1. Search strategy performed in databases CINAHL, COCHRANE CENTRAL, LILACS, LIVIVO, PUBMED, SCOPUS, WEB OF SCIENCE, GOOGLE SCHOLAR, and PROQUEST on February 13th, 2019.

Search	Search Strategy (CINAHL)	Results
#1	"phlebitis" OR "thrombophlebitis" OR "periphlebitis"	**2,020**
#2	"administration, topical" OR "ointments" OR "ointment" OR "pastes" OR "unguents" OR "skin cream" OR "skin care" OR "transdermal patch" OR "emulsions" OR "emulsion" OR "powders" OR "powder" OR "solutions" OR "skin therapy" OR "skin ointment" OR "cream" OR "skin cream" OR "creme" OR "creams" OR "gel" OR "dressing" OR "dressings" OR "lotion" OR "oil" OR "patch" OR "moisturizer" OR "topical" OR "topical route" OR "topical interventions" OR "topical application" OR "topical ointment" OR "topical agents" OR "topical treatment" OR "topical administration"	**106,868**
#3	S1 AND S2 (WITHOUT FULL TEXT MARKING)	**188**

Search	Search Strategy (COCHRANE)	Results
#1	"phlebitis" OR "periphlebitis" OR “chemical phlebitis” **Filter: Trials**	**713**
#2	"administration, topical" OR "ointments" OR "ointment" OR "pastes" OR "unguents" OR "skin cream" OR "skin care" OR "transdermal patch" OR "emulsions" OR "emulsion" OR "powders" OR "powder" OR "solutions" OR "skin therapy" OR "skin ointment" OR "cream" OR "skin cream" OR "creme" OR "creams" OR "gel" OR "dressing" OR "dressings" OR "lotion" OR "oil" OR "patch" OR "moisturizer" OR "topical" OR "topical route" OR "topical interventions" OR "topical application" OR "topical ointment" OR "topical agents" OR "topical treatment" OR "topical administration"	**161,797**

#3	**Filter: Trials** #1 AND #2 **Filter: Trials**	**194**

Search	Search Strategy (LILACS)	Results
#1	Flebite OR phlebitis OR flebitis	**5,665**
#2	Administração tópica OR topical administration OR administración tópica	**37,577**
#3	Flebite OR phlebitis OR flebitis AND Administração tópica OR topical administration OR administración tópica	**28**

Search	Search Strategy (LIVIVO)	Results
#1	phlebitis AND treatment AND prevention AND topical	**149**

Search	Search Strategy (PUBMED)	Results
#3	((#1) AND #2)	**797**
#2	("phlebitis"[MeSH Terms] OR "phlebitis" OR "chemical phlebitis" OR “periphlebitis”)	**27,345**
#1	("administration, topical"[MeSH Terms] OR “administration, topical” OR "ointments"[MeSH Terms] OR "ointments"	**1.202,101**

	OR "ointment" OR "pastes" OR "unguents" OR "skin cream" OR "skin care"[MeSH Terms] OR "skin care" OR "transdermal patch"[MeSH Terms] OR "transdermal patch" OR "emulsions"[MeSH Terms] OR "emulsions" OR "emulsion" OR "powders"[MeSH Terms] OR "powders" OR "powder" OR "solutions"[MeSH Terms] OR "solutions" OR "skin therapy" OR "skin ointment" OR “cream” OR "skin cream"[MeSH Terms] OR "skin cream" OR “creme” OR “creams” OR “gel” OR "dressing" OR "dressings” OR “lotion” OR “oil” OR "patch" OR “moisturizer” OR “topical” OR "topical route" OR "topical interventions" OR "topical application" OR "topical ointment" OR "topical agents" OR "topical treatment" OR "topical administration")

Search	Search Strategy (SCOPUS)	Results
#1	TITLE-ABS-KEY("phlebitis" OR "periphlebitis") AND ("administration, topical" OR "ointments" OR "ointment" OR "pastes" OR "unguents" OR "skin cream" OR "skin care" OR "transdermal patch" OR "emulsions" OR "emulsion" OR "powders" OR "powder" OR "solutions" OR "skin therapy" OR "skin ointment" OR "cream" OR "skin cream" OR "creme" OR "creams" OR "gel" OR "dressing" OR "dressings" OR "lotion" OR "oil" OR "patch" OR "moisturizer" OR "topical" OR "topical route" OR "topical interventions" OR "topical application" OR "topical ointment" OR "topical agents" OR "topical treatment" OR "topical administration") **Filter: Article**	**930**

Search	Search Strategy (WEB OF SCIENCE)	Results
#1	Topic: "administration, topical" OR "ointments" OR "ointment" OR "pastes" OR "unguents" OR "skin cream" OR	**2.799,672**

	"skin care" OR "transdermal patch" OR "emulsions" OR "emulsion" OR "powders" OR "powder" OR "pharmaceutical solutions" OR "solutions" OR "skin therapy" OR "skin ointment" OR "cream" OR "skin cream" OR "creme" OR "creams" OR "gel" OR "dressing" OR "dressings" OR "lotion" OR "oil" OR "patch" OR "moisturizer" OR "topical" OR "topical route" OR "topical interventions" OR "topical application" OR "topical ointment" OR "topical agents" OR "topical treatment" OR "topical administration" Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Tempo estipulado=Todos os anos	
#2	Topic: ("phlebitis" OR "periphlebitis") Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Tempo estipulado=Todos os anos	**2,340**
#3	#1 AND #2	**167**

Search	**Search Strategy (GOOGLE SCHOLAR)**	**Results**
#1	("phlebitis" OR "thrombophlebitis" OR "periphlebitis") AND ("administration, topical" OR "ointments" OR "ointment" OR "pastes" OR "unguents" OR "skin cream" OR "skin care" OR "transdermal patch" OR "emulsions" OR "emulsion" OR "powders" OR "powder" OR "solutions" OR "skin therapy" OR "skin ointment" OR "cream" OR "skin cream" OR "creme" OR "creams" OR "gel" OR "dressing" OR "dressings" OR "lotion" OR "oil" OR "patch" OR "moisturizer" OR "topical" OR "topical route" OR "topical interventions" OR "topical application" OR "topical ointment" OR "topical agents" OR "topical treatment" OR "topical administration")	**100**

Search	**Search Strategy (PROQUEST)**	**Results**

#1	("phlebitis" OR "thrombophlebitis" OR "periphlebitis") AND ("administration, topical" OR "ointments" OR "ointment" OR "pastes" OR "unguents" OR "skin cream" OR "skin care" OR "transdermal patch" OR "emulsions" OR "emulsion" OR "powders" OR "powder" OR "solutions" OR "skin therapy" OR "skin ointment" OR "cream" OR "skin cream" OR "creme" OR "creams" OR "gel" OR "dressing" OR "dressings" OR "lotion" OR "oil" OR "patch" OR "moisturizer" OR "topical" OR "topical route" OR "topical interventions" OR "topical application" OR "topical ointment" OR "topical agents" OR "topical treatment" OR "topical administration")	**100**

Appendix 2. Excluded articles and reasons for exclusion **(n=28)**

Author, year	**Reason for exclusion**
Liu, 2016; Myiajima, 2013; Nakauchi, 2015; Bagheri-Nesami, 2014; Chang, 2015; Dong, 2007; Jin, 2015; Xiao, 2004; Zheng, 2004; Ng, 2010	Original article in chinese or non-latin languages
De Sanctis, 2001	Deep vein thrombosis in lower limbs
Dobbins, 2003	Article comparing 2 different intravenous therapies
Sandor, 2005; Yang, 2008; Dal Ry, 1999; Kokotis, 1998; Li, 2003; Liu, 2015	Full text not found
Nct, 2014;	RCT protocol for unpublished trial
Berardi, 2003; Tjoon, 2000; Shamloo, 2015;	Reviews, letters, conference abstract, personal opinions, case reports, cross sectional, preclinical
Varghese and Moly, 2018; Abdollahi, 2016; Babaieasl, 2019;	Data not individualized for PIT

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Appendix 3. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	13
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	21
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	23
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	23
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	24
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	24
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	24
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	25
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	25
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	25

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	26
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	26
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	27
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	29
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	36
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	37
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	42
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	42
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	43
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	44
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	44
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-