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Contrast media extravasations in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions

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ABSTRACT

Objective: To identify risk factors and interventions preventing or reducing contrast medium extravasation.

Introduction: Computed tomography (CT) is a radiological examination essential for the diagnosis and monitoring of many diseases. It is often performed with the intravenous (IV) injection of contrast agents. Use of these products can result in a significant complication, extravasation, which is the accidental leakage of IV material into the surrounding tissue. Patients may feel a sharp pain and skin ulceration or necrosis may develop.

Inclusion criteria: This review considered studies that included patients (adults and children) undergoing a CT with IV administration of contrast media. The risk factors considered were patient demographics, comorbidities and medication history. This review also investigated any strategies related to: contrast agent, injection per se, material used for injection, apparatus used, healthcare professionals involved, and patient risk assessment performed by the radiology personnel. The comparators were other interventions or usual care. This review investigated randomized controlled trials and non-randomized controlled trials. When neither of these were available, other study designs, such as prospective and retrospective cohort studies, case-control studies and case series, were considered for inclusion. Primary outcomes considered were: extravasation frequency, volume, severity and complications.

Methods: The databases PubMed, CINAHL, Embase, the Cochrane Register of Controlled Trials, Web of Science PsycINFO, ProQuest Dissertations and Theses A&I, TRIP Database and ClinicalTrials.gov were searched to find both published and unpublished studies from 1980 to September 2016. Papers were assessed by two independent reviewers for methodological validity using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). Data were extracted using the standardized data extraction tool from JBI SUMARI. In one case, quantitative data from two cohort studies were pooled in a statistical meta-analysis. However, generally, statistical pooling was not possible due to heterogeneity of the interventions, populations of interest or outcomes. Accordingly, the findings have been presented in narrative form.

Results: Fifteen articles were selected from a total of 2151 unique studies identified. Two were randomized controlled trials and 13 were quasi-experimental and observational studies. The quality of these studies was judged to be low to moderate. Some patient characteristics, such as female sex and inpatient status, appeared to be risk factors for extravasation. Additionally, injection rate, venous access site and catheter dwelling time could affect the volume extravasated. Preliminary studies seemed to indicate the potential of extravasation detection accessories to identify extravasation and reduce the volume extravasated. The other interventions either did not result in significant reduction in the frequency/volume of extravasation, or the results were mixed across the studies.

Conclusions: The majority of the studies included in this review evaluated the outcomes of extravasation frequency and volume. Given the quality of the primary studies, this systematic review identified only potential risk factors and interventions. It further highlighted the research gap in this area and the importance of conducting trials with solid methodological designs.

Keywords contrast media; extravasation; frequency; prevention; radiology

JBI Database System Rev Implement Rep 2018; 16(1):87–116.

Summary of findings

1. Cannula type/size

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation frequency	205 (1)	⊕⊕⊖⊖ Low	Similar frequency for 18-gauge fenestrated (0%) and 20-gauge non-fenestrated catheter (0%).
	86299 (4)	⊕⊖⊖⊖ Very low	Discrepancy of the effect of cannula size depending on the studies.
Extravasation volume	289 (1)	⊕⊖⊖⊖ Very low	No significant difference between cannula sizes.
Image quality	205 (1)	⊕⊕⊖⊖ Low	No significant difference between 18-gauge fenestrated and 20-gauge non-fenestrated catheter.

2. Power injection compared to manual injection

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation frequency	3560 (1)	⊕⊖⊖⊖ Very low	Similar frequency for power (0.3%) and manual injection (0.2%).

3. Infusion rate

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation frequency	180 (1)	⊕⊕⊕⊖ Moderate	No significant difference between infusion rates.
	359222 (3)	⊕⊖⊖⊖ Very low	No significant difference between infusion rates. injection rates.
Extravasation volume	4701 (2)	⊕⊖⊖⊖ Very low	The volume varied significantly according to
Reaction to contrast media	4457 (1)	⊕⊖⊖⊖ Very low	No significant difference between infusion rates.
Injury severity	352125 (1)	⊕⊖⊖⊖ Very low	No significant difference between infusion rates.
Image quality	180 (1)	⊕⊕⊕⊖ Moderate	No significant difference between infusion rates.

4. With ultrasound guided intravenous catheter insertion (USGIV)* compared to without

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Odds Ratio (95% CI) / Relative Risk (95% CI)
Extravasation frequency	40143 (1)	⊕⊖⊖⊖ Very low	OR = 8.6 (4.6-16.2)
Injury severity	40143 (1)	⊕⊖⊖⊖ Very low	RR = 0.71 (0.25-2)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in this group and the relative effect of the intervention (and its 95% CI).

OR: Odds Ratio; CI: Confidence interval; RR: Relative Risk

5. Venous access

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation frequency	5101 (3)	⊕⊕⊖⊖ Very low	Discrepancy of the effect depending on the studies.
Extravasation volume	339 (1)	⊕⊖⊖⊖ Very low	Significant difference according to venous access: from 23.9 mL (hand) to 55.1 mL (antecubital fossa).

6. Warmed contrast media compared to that at ambient temperature

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation frequency	24820 (1)	⊕⊖⊖⊖ Very low	Discrepancy of the effect depending on the contrast media.
Extravasation volume	24820 (1)	⊕⊖⊖⊖ Very low	No significant difference.

7. Type of health professional

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation frequency	8017 (2)	⊕⊖⊖⊖ Very low	No significant difference

8. A newly inserted catheter compared to an existing catheter

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation volume	170 (1)	⊕⊖⊖⊖ Very low	Reduced volume for the new catheter: from 63.1 to 40.6 mL.

9. With a practice quality improvement project compared to without

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation frequency	163100 (1)	⊕⊖⊖⊖ Very low	No significant difference between before and after the implementation project.
Extravasation volume	163100 (1)	⊕⊖⊖⊖ Very low	No significant difference between before and after the implementation project.
Injury severity	163100 (1)	⊕⊖⊖⊖ Very low	No significant difference between before and after the implementation project.

10. With an extravasation detection accessory compared to without

Bibliography: Ding s, Meystre NR, Campeanu C, Gullo G. Contrast media extravasations among in patients undergoing computerized tomography scanning: a systematic review and meta-analysis of risk factors and interventions. JBI Database System Rev Implement Rep 2017; 16(1):87–116.

Outcomes	Number of participants (studies)	Quality of the evidence (GRADE)	Impact
Extravasation volume	1085 (1)	⊕⊖⊖⊖ Very low	Significantly more small volumes and less large ones.

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.
OR: odds ratio; CI: confidence interval; RR: relative risk

Introduction

Computed tomography (CT) is a frequently conducted radiological examination and the number performed continues to increase globally. For instance, in the United States, the popularity of CT scans more than doubled in 10 years, reaching 275 examinations per 1000 people in 2011.[1] This trend is likely to continue over the coming years due to aging of the general population and the resulting increase in chronic diseases, such as cardiovascular diseases, cancer and metabolic diseases.[2] For the diagnosis and monitoring of a large variety of diseases, CT scanning has become indispensable because of its higher sensitivity and specificity compared to

classical X-ray examinations.[3] This is an inevitable result of its capacity to produce axial images from which volumetric reconstructions can be created in three dimensions,[3] or even in four dimensions with multiple cardiac phases (cine loops).[4]

Radiological examination by CT produces an image quality that is continually improving and allows the visualization of hard tissue, such as bone, as well as parenchyma, such as liver.[5] In order to enhance differentiation of the anatomy and abnormal structures, particularly in regards to the vascular system and viscera, iodinated contrast medium is routinely injected intravenously.[6] The contrast media allow differentiation between the venous and arterial tissue phases.[5] Evidence indicates that contrast medium is used in approximately 50% of CT scans, making it a widespread practice.[7] Contrast media are traditionally administered intravenously by manual or drip injection methods. However, it has been observed that these methods have variable results in terms of injection flow rates, which may negatively affect specific organ enhancement.[8] An increasing number of radiology departments are becoming equipped with automated power injectors for the administration of contrast media through peripheral venous catheters at a constant flow rate allowing specific angiographic and visceral enhancement.[9]

The injection of radiographic contrast agents facilitates improved diagnostic or prognostic accuracy, with clearer tissue differentiation or vascular imaging owing to vessel opacification.[5] However, the development of side effects, such as allergic-like reactions, vasovagal reactions, cardiac arrhythmias and pulmonary edema is possible with the use of contrast agents.[8,10] Furthermore, a well-recognized potential complication is extravasation of the contrast medium,[11] which is defined as the accidental leakage of injected fluid into the surrounding tissue.[12] The expanded use of power injectors in lieu of manual or drip injection increases the risk of extravasation.[13,14] Because contrast media are vesicants, this can result in injury to the patient. In the best-case scenario, the adverse effects are mild, resulting in no severe sequelae, e.g. inflammatory reactions,[14,15] but extravasation nevertheless causes pain and discomfort to the patient that may persist in the long term. Major adverse reactions such as skin ulceration, soft-tissue necrosis, and compartment syndrome have all been documented.[16] Serious side effects are a risk, regardless of whether ionic or non-ionic contrast media are used.[16]

When extravasation does occur, it is important to monitor the patient closely for the development of symptoms because the reaction manifests itself several hours after injection and the duration of clinical signs may vary substantially.[8] For the treatment of serious extravasation, a surgical fasciotomy, skin grafting or even amputation may be required.[8,14,17,18]

Furthermore, if complications associated with extravasation occur, the CT scan may be delayed and new intravenous (IV) access must be secured, causing additional stress to the patient, on top of the known stressors associated with a CT scan.[19-21] Sometimes the CT scan itself must be repeated, which exposes the patient to additional radiation and contravenes the "As Low As Reasonably Achievable" (ALARA) principle of radiation protection.[22] A second injection of contrast increases costs due to the material injected,[19] the radiology personnel required, and the scanner utilization. It also reduces the radiological department workflow.[19] As such, the financial and social implications of extravasation are meaningful.

Certain patient characteristics may be associated with an increased risk of extravasation. This is the case for patients with diabetes mellitus, venous thromboembolism, cancer or altered communication (young children, elderly, debilitated or unconscious patients).[8,10,13,14] Furthermore, several factors related to healthcare professionals and medical equipment used affect the risk of extravasation. Intravenous injections may be administered by persons with different qualifications: they may be nurses, radiographers or radiologists. Researchers have investigated whether this may affect the risk of extravasation.[23] Additionally, training or the lack thereof of the healthcare professional may be an important variable, and be used to detect patients at risk.[9,24]

Several prevention methods have been reported in the literature; these are related to the characteristics of the contrast media (including volume, concentration, viscosity, temperature, and rate of administration)[6,8,13,23,25-28] as these have been shown to either increase or decrease extravasation (rate and volume). Similarly, the apparatus

used for injection (catheter gauge, cannulas, butterfly, venflon)[6,13,23,25,26,28] and the injection technique (patient injection site, preparation room)[13,14,25,26,28] may affect the risk of extravasation. In regards to the preparation room, it can be argued that a quiet environment limits the risk of extravasation. Finally, the risk of extravasation could potentially be reduced through the use of a newly developed extravasation detection apparatus (detection device: ultrasound, radiofrequency).[29]

It is especially important for radiology personnel to know the effectiveness of these different methods as they can apply, in their clinical practice, those most likely to prevent extravasation. This should also help to improve the patient's experience when undergoing CT. Moreover, identification of risk factors should contribute to a reduction in the occurrence of extravasation. Primary research has been published, whether on risk factors or on strategies for the prevention of extravasation, and has increased in recent years, as evidenced by the number of publications available. In addition, guidelines have been published by learned societies such as the American College of Radiology[8] and the European Society of Urogenital Radiology,[11] however, these are not based on systematic literature reviews. Therefore, a systematic review of literature on the subject would be meaningful. A search of the *JBI Database of Systematic Reviews and Implementation Reports*, Cochrane Library, MEDLINE and TRIP database by the authors yielded no systematic review on the scientific evidence associated with these risk factors and interventions. Therefore, it is beneficial and worthwhile to conduct a systematic review of the data associated with the prevention of contrast media extravasation during CT examination. The systematic review was conducted according to an *a priori* published protocol.[30] The current review has a focus on risk factors implicit as a component of patient risk assessment. Furthermore, the search strategy regarding published and unpublished studies was very broad and included the risk factors, as did our selection process of the articles. Accordingly, this variation of the previously published protocol could not introduce bias.

Review question

The primary objective of the review was to identify risk factors and interventions that prevent or reduce the extravasation of contrast medium in patients undergoing CT examination.

Inclusion criteria
Participants
This review considered studies that included patients (adults or children) undergoing a CT examination, for any indication and of any part of the body, that required the use of IV contrast media. The examination could be either a classical CT or an interventional radiology CT procedure. The participants could be either hospitalized or outpatients.

This review did not explore studies involving extravasation in the context of chemotherapy, anesthesia, or parenteral nutrition. Indeed, the products used in those contexts are of a very different composition and thus possessed different properties (e.g. viscosity and toxicity) as compared to contrast media.

Risk factors/interventions
This review evaluated patient-related risk factors, i.e. patient demographics, comorbidities and medication history. Consideration was also given to studies that evaluated interventions or protocols that might prevent extravasation of contrast media or reduce the damage associated with it. Accordingly, the review investigated any strategies related to:
- Contrast agent (volume, concentration, viscosity, temperature)
- Injection per se (patient injection site, preparation room)
- Material used for injection (catheter gauge, cannulas, butterfly, venflon)
- Apparatus used (extravasation detection device: ultrasound, radiofrequency)
- Healthcare professionals (profession, skill level)
- Patient risk assessment by the radiology personnel (medication, morbidity, language).

Comparator
The comparators of this study were either other patient characteristics, other interventions (different contrast agent, different cannula), or usual care (the absence of a preparation room or extravasation detection device).

Outcomes
This review included studies that focused on primary and/or secondary outcomes described below.

Primary patient outcomes:

- Extravasation frequency, as evidenced by inspection of the injection site during and/or after the CT exam.
- Extravasation volume, as evidenced by the extent of the swelling at the injection site and/or by noting the injected volume on the power injector.
- Extravasation severity, including:
  - inflammatory reactions, necrosis as evidenced by inspection of the injection site
  - pain or discomfort, information obtained through questioning or self-reporting by the patient.
- Treatment of complications, including plastic surgery and amputation, generally reported by the plastic surgeon and/or found in a critical incident reporting system.

Secondary outcomes:

- Diagnostic value and accuracy, measured by the enhancement level or subjective image quality.
- Workflow, measured by the number of CT scans performed over a given time period.
- False positive detection of extravasation. This outcome was specific to the interventions using a detection device.

Types of studies

This review considered experimental study designs such as randomized controlled trials and non-randomized controlled trials. In the absence of these trials, other study designs, such as prospective and retrospective cohort studies and case-control studies were examined for inclusion. In the absence of significant analytical literature on the topic, descriptive epidemiological study designs including case series, individual case reports, and descriptive cross-sectional studies were considered for inclusion.

Methods
Search strategy

The search was conducted to find both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of MEDLINE and CINAHL was performed, followed by analysis of the words contained in the retrieved titles and abstracts and of the index terms used to describe the article. A second search using all identified keywords and index terms was then conducted to include all databases (Appendix I). Thirdly, the list of

all identified reports and articles was searched for additional qualifying studies. Studies published in both English and French between 1980 and September 2016 were examined for inclusion in this review. The lower limit of 1980 was chosen because we were aware of a publication, from 1986, on this topic.[31]

The databases that were searched included: CINAHL, Embase, PubMed, the Cochrane Register of Controlled Trials, Web of Science and PsycINFO.

The search for unpublished studies included: ProQuest Dissertations and Theses A&I, TRIP Database and ClinicalTrials.gov registry.

Initial keywords used were: extravasation, contrast media, computed tomography, prevention, healthcare professionals, frequency, volume, complications.

Assessment of methodological quality

Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI).[30] Any disagreements between the reviewers were resolved through discussion, or with the involvement of a third reviewer.

Data extraction

Data were extracted from papers included in the review using the standardized data extraction tool from JBI SUMARI.[30] The information extracted included details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. For further clarification, the author of one of the primary studies was contacted, but this was to no avail.[32]

Data synthesis

The primary objective was to pool all the quantitative data for statistical meta-analysis. The results were subject to double data entry by the two reviewers. A meta-analysis was performed using RevMan (Copenhagen: The Nordic Cochrane Centre, Cochrane).[33] Effect sizes (expressed as an odds ratio for categorical data) and their 95% confidence intervals were calculated for analysis. Heterogeneity was assessed using the standard Chi-square and I^2 tests. Where statistical pooling was not possible, the findings were presented in narrative form including a table to aid in data presentation.

Results

Study selection

A total of 2299 relevant citations were found following the bibliographic search of each database. In addition, two studies[34,35] were retrieved by consulting the reference lists of the articles. Using Endnote (Clarivate Analytics, PA, USA), 150 articles were identified as duplicates, resulting in 2151 unique publications. Those were screened by the reviewers based on the title and abstract and 2106 articles were excluded. The main reasons for exclusion were that the publications were not relevant or that they did not present data on human subjects. An additional 21 studies were excluded after reading the full-text articles. These were excluded, for instance, because of a lack of data on the ratio of extravasation per population group or per intervention, or because no real contrast media was used. The methodological quality of the 24 remaining articles was evaluated by the reviewers using the critical appraisal checklist from the Joanna Briggs Institute.[30] Nine additional articles were excluded following assessment of the methodological quality. The main reasons for excluding citations at this stage were the absence of a comparison group or the presence of confounding variables. The excluded studies and the reasons for their exclusion are listed in Appendix II. Finally, both reviewers agreed that the quality of 15 articles was sufficient to include them in this systematic review. Figure 1 details the process of article selection.
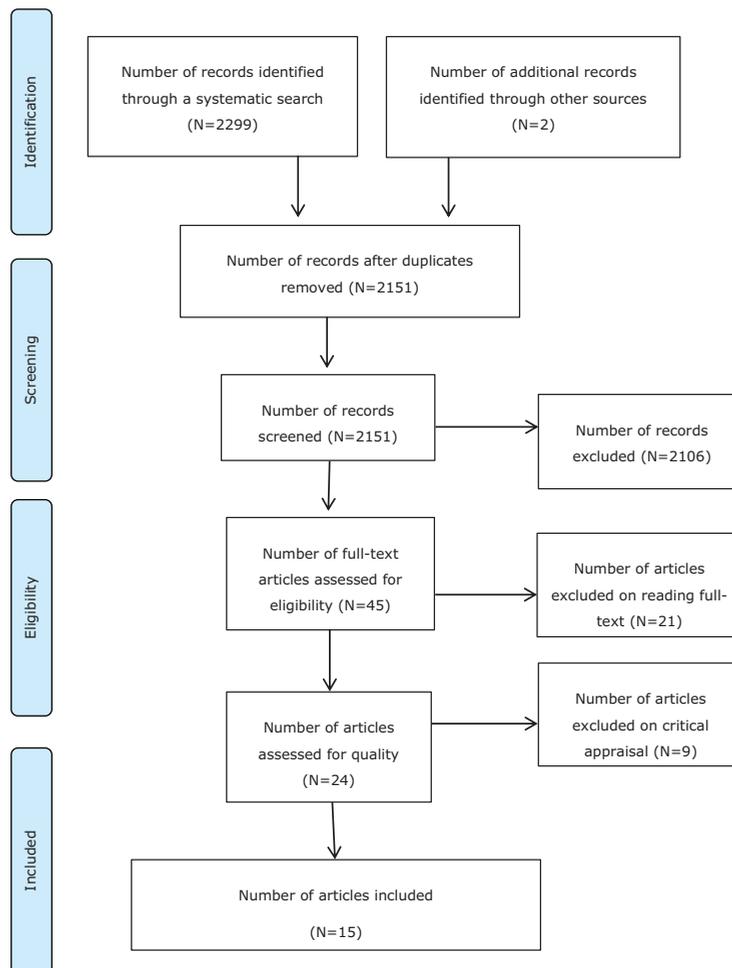
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med* 6(6): e1000097.

Figure 1: Flowchart of study selection and inclusion process

Among the citations that had data on the relevant outcomes, there was one randomized control trial,[37] one pseudo-randomized trial,[36] one quasi-experimental trial,[19] and one pre-post study,[31] with the remainder being cohort[9,23,26,27,28,34,40,42] or case series designs.[38,39,41] Studies other than clinical trials were included when they related to a different outcome, population of interest or intervention. The characteristics of the included studies are detailed in Appendix III.

Methodological quality

The critical appraisal scores were calculated using the checklist from the Joanna Briggs Institute[30] for two randomized trials and 13 quasi-experimental and observational studies; they are provided in Tables 1 and 2, respectively. The quality of the randomized trials was judged as moderate with scores of 7 and 8 out of 10 (Table 1). The study with the lowest score was a pseudo-randomized trial with 33 of the patients allocated to the larger cannula group being eliminated because of vessel fragility. This did not occur in the other arm of the trial. Therefore, the two arms, containing roughly 100 patients each, were not strictly comparable. It was also unclear whether those assessing outcomes were blinded to the treatment allocation. The assessor appeared to be blinded to the outcomes pertaining to image quality, but not to the extravasation event.

For the observational studies, the lowest recorded score was 3 while the highest was 7 out of a total of 9, indicating that the quality of those studies was low to moderate. In all articles, follow-up was performed

Table 1: Assessment of methodological quality of included randomized trials

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
Johnson et al.[36]	Y	Y	U	Y	U	N	Y	Y	Y	Y	7/10
Kok et al.[37]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8/10

N, No; U, Unclear; Y, Yes.

Table 2: Assessment of methodological quality of included quasi-experimental and observational studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
Amaral et al.[9]	Y	Y	Y	U	Y	Y	NA	Y	NA	6/9
Birnbaum et al.[38]	Y	Y	NA	Y	NA	Y	NA	Y	NA	5/9
Davenport et al.[27]	Y	Y	Y	N	Y	Y	NA	Y	Y	7/9
Dykes et al.[32]	Y	Y	Y	N	Y	Y	N	Y	Y	7/9
Hoff et al.[39]	U	N	Y	U	NA	Y	NA	Y	NA	3/9
Johnson et al.[34]	Y	Y	Y	U	U	Y	N	U	NA	4/9
Moreno et al.[28]	Y	Y	Y	N	Y	Y	N	Y	U	6/9
Rupp et al.[40]	Y	Y	N	U	Y	Y	NA	Y	Y	6/9
Saade and Brennan[41]	U	Y	NA	Y	NA	Y	NA	Y	NA	4/9
Schwab et al.[19]	Y	Y	Y	Y	U	Y	Y	U	NA	6/9
Shaqdan et al.[42]	Y	Y	N	Y	Y	Y	NA	Y	Y	7/9
Sinan et al.[23]	Y	Y	Y	N	Y	Y	NA	Y	Y	7/9
Wienbeck et al.[26]	Y	Y	N	Y	Y	Y	NA	Y	U	6/9

N, No; NA, Not applicable; U, Unclear; Y, Yes.

over a sufficient period of time. Additionally, in most of the studies, the outcome measurements were judged to be reliable and of good quality, corresponding to the current clinical practices. This constitutes one of the strengths of the studies. As indicated by the answers to the ninth question, the statistical analyses were also appropriate, even though they could have been more clearly described in two articles and that a more complex analysis could have been performed in most articles. However, the quality was lower for the management of confounding variables and selection bias. Several different contrast media were used in the studies, resulting in heterogeneity. In some articles, no information was provided regarding the type of contrast material used. However, because extravasation is detected immediately following IV injection, no loss of follow-up occurred. This constitutes another major strength of this systematic review.

Characteristics of included studies

The studies included in this systematic review investigating the prevention of and reduction in the severity of contrast media extravasation are presented in Appendix III. Of the 15 included studies, only two were randomized trials, while 13 were quasi-experimental and observational studies. The majority of the articles dealt with extravasation in adults, while one study focused on adults and children together and another focused on children only. The most frequently studied risk factor was patient demographics. A variety of interventions were considered in these studies such as the cannula, contrast media, injection (including the extravasation detection accessory), and the health professional injecting the medium. The outcomes measured in these studies were extravasation frequency and volume, complications and image quality. None of the studies investigated the effect of interventions on workflow.

The results have been presented according to the type of intervention.

Findings
Risk factors for extravasation
Patient gender
In the literature, this variable was considered in relation with two outcomes: extravasation frequency[26,40,42] and volume of extravasate.[28]

The data from two cohort studies[26,42] on the risk of extravasation depending on the gender of the patient were grouped together in a meta-analysis performed with RevMan (Copenhagen: The Nordic Cochrane Centre, Cochrane).[33] We used a generic inverse variance method recommended for non-randomized studies.[43] For a total of 356,582 individuals, the calculated odds ratio (OR) was 1.37 (95% CI: 1.15–1.64) (Figure 2). This indicates a significantly lower extravasation risk in males as compared to females ($P < 0.001$). No statistically significant heterogeneity was detected with a Chi-square value of 0.89 ($P = 0.35$) and an I^2 of 0%. The effect of gender was also emphasized in a multivariate logistic regression by Rupp et al.[40] Being a female was associated with an increased risk of extravasation, as indicated by the adjusted odds ratio of 1.8 (95% CI: 1.1–2.9).

However, the gender of the patient did not seem to have an impact on the volume of contrast media extravasated ($P = 0.81$), as indicated in a study performed by Moreno et al.[28] For 93 men, the mean volume of extravasated material was 53.2 mL ± 41.6, and for 137 women it was 51.9 ± 40.9.

Patient age
Three studies investigated patient age as a potential risk factor for extravasation. Two of the studies considered the impact of age on extravasation frequency,[26,42] while the third study evaluated the
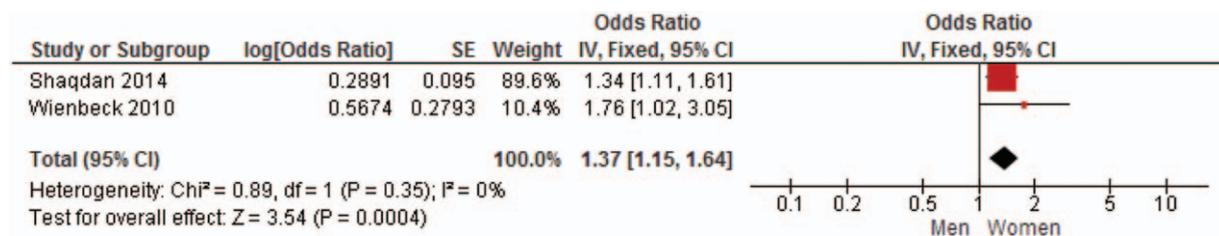

Figure 2: Meta-analysis of the extravasation frequency in men and women in cohort studies (CI: confidence interval; SE: standard error)

volume of extravasate.[28] Due to heterogeneity in the interventions and outcome, no meta-analysis could be performed and the results have been presented as a narrative.

When separating the adult patients in two age groups, Wienbeck et al.[26] showed that extravasations occurred more frequently in older patients (>50 years) as compared to younger ones (≤50 years). The difference was statistically significant with rates of 1.4% and 0.6%, respectively ($P = 0.019$).

However, the study by Shaqdan et al.[42] revealed no statistical difference in the rate of extravasation between adults aged 18 to 60 years (0.12%) and adults over 60 years (0.14%; $P = 0.12$). The difference remained non-significant when children (<18 years) were added as a third group (0.12%; $P = 0.29$).

To study the outcome "volume of extravasate", Moreno et al.[28] considered four age groups. The average amount of contrast material extravasated was slightly higher for persons aged 18–39 years (58.1 mL ± 44.1; n = 42) than it was for patients of at least 80 years (48.7 mL ± 35.5; n = 46). For the patients of intermediate ages, 40–59 years and 60–79 years, the volume of extravasate was intermediate at 51.8 mL (± 38.7; n = 108) and 51.9 mL (± 43.1; n = 124), respectively. Nevertheless, the difference between the four groups was not statistically significant ($P = 0.83$).

Patient specificity

Three studies investigated the specificities of the patient, in one case comparing patients from a cancer center with those from an outpatient center,[34] and in another case comparing inpatients and outpatients.[42] The third study focused on episodes of hospitalization in the previous year and intravenous drug use.[40] Because of this heterogeneity, we did not perform a meta-analysis.

In a prospective cohort study, Johnson et al.[34] compared the number of extravasations in two populations of patients. Four extravasations were noted in 495 patients from the cancer center, while two extravasations were noted in patients from the outpatient center (n = 498). This suggested a similar risk of extravasation between the two groups. Catheter placement was performed in the radiology department for both groups.

Shaqdan et al.[42] reported that the occurrence of extravasation in adults and children was higher for

inpatients (160/54664) than it was for outpatients (291/297461; $P < 0.0001$).

According to a recent study, the patients at highest risk of extravasation are those recently hospitalized (adjusted OR = 2.0; 95% CI: 1.3–3.1) or with a history of IV drug use (adjusted OR = 5.8; 95% CI: 1.7–19.9).[40]

Interventions
Cannula

Six studies investigated the effect of catheter gauge on extravasation frequency and volume, injury severity or image quality. Only one of these was a pseudo-randomized trial;[36] it has been presented separately because the catheters were different from the type used in the other studies. Johnson et al.[36] compared fenestrated to non-fenestrated catheters. All the studies evaluated adults, except one by Amaral et al.[9] that was performed on children. Because the interventions and/or populations of interest differed between these studies, no meta-analysis could be performed.

Fenestrated versus non-fenestrated cannula in adults

One study compared an 18-gauge fenestrated (18G-F) catheter to a 20-gauge non-fenestrated (20G-NF) catheter for the injection of intravenous contrast media.[36] A total of 205 injections were performed, including 103 with the 18G-F catheter and 102 with the 20G-NF catheter. No difference in rate of extravasation was detected between the two groups, with none being noted in either case. Image quality was assessed via two approaches: a subjective evaluation by a radiologist and a measurement of the aortic enhancement level. The subjective evaluation of image quality indicated that all images in both groups were acceptable. The measured enhancement levels were not significantly different between the two groups, when compared by anatomic region ($P = 0.45$–0.91).

Cannula in adults

Two cohort studies and one quasi-experimental study investigated the effect of cannula size on frequency of extravasation in adult patients.[19,23,26]

In a retrospective cohort study, Wienbeck et al.[26] analyzed the administration of contrast media in 4457 patients. The non-ionic contrast media was administered using an injector with five different catheter sizes. The reported extravasation frequency

was 0/9 for the 24-gauge (24G), 14/696 for the 22-gauge (22G), 29/2996 for the 20-gauge (20G), 8/746 for the 18-gauge (18G), and 0/10 for the 16-gauge (16G) catheters. Significantly more extravasations occurred with use of the 22G (2.2%) catheter as compared to the 20G (1%) and 18G (1.1%) ($P < 0.05$).

In a study performed by Sinan et al.,[23] 2640 adults were injected with nonionic contrast media using a power injector. Of the 1136 injections performed with an 18G catheter, four extravasations occurred. Similarly, of the 1504 injections performed with a 20G catheter, five extravasations occurred, revealing no significant effect of cannula size on extravasation frequency ($P > 0.05$). When the contrast medium was manually injected in 920 adults, no difference was again noted between the 18G and 20G catheters.[23]

Schwab et al.[19] reported the results of 58 patients who were administered contrast media with a power injector. The injection was performed using a 20G catheter at 5 mL/sec (N = 26) or a 22G catheter at 3 mL/sec (N = 32). No significant difference was observed between the two groups ($P > 0.05$) with 2 and 0 extravasations occurring, respectively.

In the retrospective cohort study performed by Moreno et al.,[28] the effect of catheter caliber was investigated in 289 adult patients. It was shown that catheter gauges of 18 (n = 33), 20 (n = 240), and 22 (n = 16) did not induce significantly different volumes of extravasate at 59.7 mL, 50.5 mL, and 29.7 mL ($P = 0.14$), respectively.

Cannula in children

In a prospective cohort study performed at a tertiary pediatric center, 554 children ranging in age from 13 days to 20 years (9.79 ± 5.05 years) were monitored.[9] They underwent a body CT or CT angiography with a power injector. Nonionic, low osmolarity contrast medium was injected using a 16G (n = 1), 18G (n = 11), 20G (n = 20), 22G (n = 444), and 24G angiocatheters (n = 78). Only two episodes of extravasation occurred, one with a 20G and the other with a 22G catheter, indicating no difference between the cannula sizes in the frequency of extravasation.

Manual versus power injection

Sinan et al.[23] evaluated whether power injection was safe as compared to manual injection. It appeared to be safe with extravasation rates of 0.3% and 0.2%, respectively ($P > 0.05$).

Infusion rate

Six publications addressed the issue of infusion rate. The population considered in one of them included both adults and children,[42] whereas the other studies concentrated on adults only.[19,23,26,28,37] The study of Schwab et al.,[19] mentioned previously for catheter size, also considered the variable of "infusion rate". The two variables cannot be separated since the infusions were either performed with a large cannula and a high flow rate or a small cannula and a low flow rate, therefore, the results of this study were not considered here again. The other studies have been summarized narratively since a meta-analysis was not possible due to the existence of different interventions, population constitutions and/or outcomes between the studies.

Infusion rate in adults

A recently published double-blind, randomized, controlled trial investigated the effect of flow rate combined with a specific contrast media concentration on the frequency of extravasation and the diagnostic value of the images.[37] Patients were randomly assigned to one of three groups: patients in group 1 (n = 63) were injected with iopromide 240 mg I/mL at 8.3 mL/s, patients in group 2 (n = 55) were injected with 300 mg I/mL at 6.7 mL/s, and patients in group 3 (n = 62) were injected with 370 mg I/mL at 5.4 mL/s, so that the iodine delivery rate and load remained constant. The extravasation frequency was found to be similar in the three groups, with no extravasation events noted. Furthermore, the diagnostic value of the images, evaluated by the Hounsfield enhancement level, was not significantly different between the three groups (group 1: 437 ± 104 HU, group 2: 448 ± 111 HU, group 3: 447 ± 106 HU: p ≥ 0.18).

A total of 2640 power injections were considered in the study performed by Sinan et al.[23] For injections with an 18G cannula, they recorded one extravasation out of 310 injections (0.3%) with a flow rate of up to 2.9 mL/s and three extravasations out of 826 injections with a flow rate of 3–4 mL/s (0.3%). No statistical difference ($P > 0.05$) was found between two groups injected with an 18G cannula (0.3% for up to 2.9 mL/s and 0.3% for 3–4 mL/s). Similarly, no statistical difference ($P > 0.05$)

was observed between two groups injected with a 20G cannula (0.2% for up to 2.9 mL/s and 0.3% for 3–4 mL/s).

In the study performed by Wienbeck et al.,[26] the rate of administration of contrast medium was divided into three groups as follows: group 1: 1–2.9 mL/s (n = 1140 injections), group 2: 3–4.9 mL/s (n = 2536), group 3: 5–8 mL/s (n = 781). No statistically significant difference was found between the groups in regards to extravasation frequency ($P = 0.95$) or in the reaction to contrast medium ($P = 0.27$). However, a significant difference was observed in the volume of extravasate. A higher injection rate led to a larger volume of extravasate: group 1: 41.3 mL, group 2: 72.6 mL, group 3: 92 mL ($P = 0.02$).

The effect of infusion rate on the volume of extravasate was also considered in the study by Moreno et al.[28] Rates of 2 mL/s (n = 31), 3 mL/s (n = 120), 4 mL/s (n = 80), and 5 mL/s (n = 13) led to significantly different volumes of extravasate ($P = 0.04$).

Infusion rate in children and adults
A total of 3309 children (<18 years) and 348,816 adults undergoing CT examination were followed in the USA.[42] The injections were performed with a power injector and separated into three groups according to the infusion rate: <2 mL/s (L), 2–3 mL/s (M), and >3 mL/s (H). The extravasation frequencies for these three groups were L: 18/11522 (0.16%), M: 363/274785 (0.13%), and H: 70/65818 (0.11%). No significant difference was detected between the groups with regard to frequency of extravasation (p > 0.05). Of the 541 extravasations, 35 patients were not harmed (L: 1, M: 31, H: 2), 415 suffered from a minor, temporary injury (L: 17, M: 330, H: 68), and one patient from the medium infusion rate suffered a major injury. The distribution of injury severity between the groups did not indicate an effect of infusion rate.

Ultrasound guided intravenous catheter insertion
A retrospective, observational study tested the effect of ultrasound-guided intravenous catheter (USGIV) insertion, as compared to standard insertion, on the frequency of contrast media extravasation and the rate of complications.[40] With USGIV insertion, the extravasation frequency was 3.6% (13/364), while it was 0.3% (102/39779) with standard insertion.

However, the participants in the two groups were not randomly selected. Indeed, USGIV was possibly used following failure of IV catheter insertion. The authors performed a multivariate logistic regression integrating covariates such as age, gender, and the presence of active chemotherapy or vascular disease. The adjusted odds ratio obtained was 8.6 (95% CI: 4.6–16.2), suggesting an increased risk of extravasation with USGIV.

Concerning the severity of extravasation, no difference was observed between the USGIV group and the standard group.[40] Indeed, a plastic surgery consultation was indicated in 23% and 32% of extravasation events respectively (relative risk = 0.71, 95% CI: 0.25 to 2.00) and none of the events actually required surgery.

Venous access location
The location of venous access was investigated in adults in three articles, in relation with either the extravasation frequency[19,26] or the volume of contrast extravasated.[28] It was additionally considered in children in another study with extravasation frequency as the outcome.[9] Since the interventions used, the population considered, and/or the outcomes recorded were different, no meta-analysis could be performed.

Venous access in adults
Wienbeck et al.[26] pointed out a higher rate of extravasation when venous access was the dorsum of the hand (13/725: 1.8%) as compared to the antecubital fossa (23/2751: 0.8%; $P = 0.018$). The other injection sites investigated were the forearm (16/955: 1.6%) and the foot (0/26: 0%). It should nevertheless be noted that the populations of the different groups might not have had the same constitution. Hence, the preferred injection site was the antecubital fossa, while the hand and the forearm were used for patients with critical venous access, such as dialysis patients.

In the study performed by Schwab et al.,[19] when considering the 56 injections performed with 22G catheters at 3 mL/s and 20G catheters at 5 mL/s, only two extravasations were noted, suggesting no effect of the injection site on rate of extravasation. The sites of venous access when the extravasation occurred were the antecubital fossa (1/31) and the wrist (1/3). No extravasation arose at the forearm (n = 13) and hand (n = 9).

As showed by Moreno et al.,[28] the volume of extravasate differed significantly between various sites of venous access ($P < 0.05$). The mean volume of extravasate was found to be 23.9 mL for the hand (n = 9), 34.9 mL for the wrist (n = 15), 48.2 mL for the arm (n = 112), and 55.1 mL for the antecubital fossa (n = 203).

Venous access in children
Among the 553 children evaluated in a study by Amaral et al.,[9] the injection site was the elbow in 119 patients, the forearm in 40, the hand in 373, and the foot in 21. A total of two extravasations was observed when the venous access site was the forearm or the hand. This suggests the existence of no difference between the four groups in regard to extravasation frequency.

Warming of contrast media
A retrospective cohort study evaluated the influence of warming of the contrast media to 37°C prior to injection on the risk of extravasation.[27] The authors considered two low-osmolality contrast materials: iopamidol 300 (Bracco Diagnostics) and iopamidol 370 (Bracco Diagnostics). For iopamidol 300, the extravasation frequency was 0.30% (32/10831) with warming and 0.23% (23/10064) without, denoting no effect of warming on this outcome ($P = 0.64$). Similarly, warming of iopamidol 300 did not seem to influence the extravasated volume ($P = 0.59$): with warming, the mean volume was 49 mL (range 10–150) and without, it was 56 mL (range 3–150). On the contrary, for iopamidol 370, warming significantly decreased the risk of extravasation ($P = 0.05$). With warming, the extravasation frequency was 0.27% (5/1851) and without, it was 0.87% (18/2074). However, as for iopamidol 300, warming of iopamidol 370 did not seem to decrease the volume of extravasate ($P = 0.76$): a mean volume of 47 mL (range 30–75) with warming compared to a mean volume of 43 mL (range 15–80) without warming.

Health professional
The effect of the health professional administering the contrast media on the frequency of extravasation was studied in adults by Sinan et al.[23] and Wienbeck et al.[26] Sinan et al. considered the affiliation of the professional in the radiology setting, whereas Wienbeck et al.[26] was interested in professional expertise.

A narrative summary of the results of the two studies is detailed below.

The fact that the professional was affiliated with the radiology department had no influence on the rate of extravasation ($P > 0.05$).[23] For power injections, the rates of extravasation were 0.2% (4/1519) when the catheter was inserted by a member of the radiology staff and 0.3% when it was inserted by another health professional (4/1107). For manual injection, no difference in the rate of extravasation was observed between radiology and non-radiology staff members ($P > 0.05$).[23]

Similarly, the experience of the health professional was shown to not affect the extravasation frequency ($P = 0.91$).[26] For medical students, residents or staff radiologists and interns, the extravasation frequencies were 1.2%, 1.1% and 1.3%, respectively.

Catheter dwelling time
The time of cannula insertion impacted the volume of extravasate ($P = 0.0005$), as presented in a cohort study by Moreno et al.[28] The mean volume of extravasate was larger for a pre-existing catheter (63.1 ± 44.5 mL, n = 80), although the flush efficacy was confirmed prior to injection of contrast. For comparison, a new catheter had a mean extravasation volume of 40.6 ± 37.9 mL (n = 90).

Practice quality improvement project
Dykes et al.[32] performed a multi-institutional study in the USA to investigate the influence of a practice quality improvement project on the risk of extravasation. For this project, radiology facilities were asked to report data related to extravasations over a six-month period. Educational materials on current knowledge regarding extravasations were then provided. Finally, the radiology facilities reported their data related to extravasations over a second six-month period. A reduced rate of extravasation was observed from the first (0.28%: 469/166193) to the second time period (0.23%: 374/163100), however the difference was not statistically significant. The distribution of the extravasated volumes was also similar between the two periods. Consequently, the frequencies of small and large volume of extravasations were comparable. Similarly, the distribution of injuries (mild, moderate, severe) was equivalent between the first and second time periods.

Extravasation detection accessory

A pre-/post-intervention study[32] and three case studies[38,39,41] investigated the effectiveness of accessories to detect extravasation and terminate the injection. These studies involved adults. The first article[32] considered several different extravasation detection accessories (EDAs) and each of the three case studies investigated a different accessory. Because of this heterogeneity the results have been reported with a narrative summary.

In a multi-center study,[32] the influence of using EDAs on extravasated volumes was analyzed. The use of EDAs modified the distribution of these volumes, with proportionally more small volumes and less large ones ($P = 0.05$).

The extravasation detection efficacy of the MEDRAD XDS contrast extravasation detector (XDS: Warrendale, PA, USA) was evaluated in a case study.[41] This apparatus uses the radio frequency permittivity method, and in case of an abnormal signal, an alarm warns the operator. Twenty-five adults were chosen because of a high risk of extravasation. All five extravasation events were detected by the EDA after the administration of 5–8 mL of contrast media.

A continuous wave Doppler ultrasound, named *SimpliDetect*, was developed by the company Neorad AS (Norway). It is an EDA that monitors blood flow both with and without the injection of contrast media. Connected to the injection pump, it interrupts the injection in case of a complication. It was used in the study by Hoff et al.[39] to monitor extravasations amongst other errors occurring during injection. Of 198 patients, this ultrasound unit detected four injection problems, including one extravasation.

Birnbaum et al.[38] used an EDA composed of a patch with an electrode placed on the skin above the injection site. The EDA is connected to a power injector and is based on electrical impedance. Abnormal changes in the impedance allow the identification of extravasations. In a total of 500 injected patients, the sensitivity of detecting extravasation larger than 10 mL was 100% (95% CI: 51% – 100%) and the specificity 98% (95% CI: 96% – 99%).

Discussion

Extravasation constitutes an adverse event with a generally low frequency in CT clinical practice. The reported extravasation frequency in the selected studies ranged from 0% to 7.7%. However, because the diagnostic value of CT examinations is highly important, the number of CT scans performed in radiology settings is high and extravasations are by far not a rare event in hospitals. Thus, identifying risk factors and effective strategies to prevent extravasation constitutes a priority. This was the objective of this systematic review, which included 15 studies. Most were observational studies, with limited methodological quality. Randomized controlled trials constitute the primary studies of choice for inclusion in quantitative systematic reviews that measure the effectiveness of an intervention. However, studying extravasation with this type of design is difficult. Only two randomized trials were found, of which one was pseudo-randomized.[36] The studies included in this review differed according to intervention, patient population and/or the outcomes, creating heterogeneity and difficulty in computing the data of several studies in meta-analyses. Only one meta-analysis could be conducted. Therefore, no strong conclusion can be drawn from these studies. However, this systematic review presents the best actual knowledge on the topic and thus can serve as a guide for clinical practice. The results are discussed according to outcomes.

Extravasation frequency

Older patients (>50 years) were found to be at higher risk of extravasation than younger patients (≤50 years).[26] This could be explained by the fact that older people often have more fragile veins and circulatory insufficiency. They might also have more health problems (e.g. cancer and diabetes) and more difficulties to communicate and make health professionals understand their pain. However, this result was not supported by the result of a smaller cohort study that compared people older and younger than 60 years.[42]

The meta-analysis pointed out a higher risk of extravasation for women than for men.[26,42] This effect may result from confounding factors. Age could be one of the factors if, for example, age was higher in the female population than in the male population. However, this was not the case in the study of Shaqdan et al.,[42] but this was not tested in the one of Wienbeck et al.[26] Another hypothesis could be that the health condition of the female population was poorer than that of the male population, for instance, when more inpatients

were women than men. Hence, Shaqdan et al.[42] reported a higher frequency of extravasation in inpatients than in outpatients. However, in their sample, the inpatients were predominantly men. Thus, this argument cannot explain the higher frequency of extravasation in women, at least in this study. Furthermore, in another study, the extravasation rate was found to be similar between outpatients and cancer patients.[34] Nevertheless, a multivariate logistic regression indicated that female gender, hospitalization in the last year, and IV drug use might constitute extravasation risk factors.[40]

Similar rates of extravasation were observed in a randomized trial between fenestrated 18G and non-fenestrated 20G catheters.[36] This result is strengthened by the fact that no significant difference was detected between the two groups in terms of sex, age and body mass index of the participants and contrast volume. The two groups may however differ by their venous quality. In addition, a comparison between the two groups in terms of comorbidities (diabetes, cardiac problem, and chemotherapy) would have been useful.

Overall, in the retrieved studies, the extravasation frequency was not affected by the cannula size in adults[19,23] nor in children.[9] Only the study of Wienbeck et al.[26] pointed out significantly more extravasations with 22G than with 20G and 18G. The studies included in this review did not consider the influence of the constituent material of the needle (plastic versus metal) on the incidence of extravasation. This could, however, be interesting to investigate, as has been proposed in an exploratory study not included in this review.[44] Furthermore, the difference in rigidity between the two plastic catheters may also constitute a promising intervention for future research, as different extravasation rates were observed in the authors' personal experience.

In relation to the choice of catheter size, it is interesting to note that the authors found a relationship between the number of attempts and the time required to prick. Accordingly, multiple sticks were more often necessary when thin catheters were chosen over large ones ($P < 0.001$ for 24G, 22G, 20G and 18G).[34] The same authors did not find a significant difference in the number of attempts between fenestrated 18G and non-fenestrated 20G catheters, but the magnitude in catheter size was lower.[36] Furthermore, when the catheter gauge increased, the time necessary to sting also increased

($P < 0.001$), with the extreme mean time of 433 ± 370 seconds for 24G and 41 ± 33 seconds for 18G.[34] Nevertheless, these results should be interpreted with great caution as there might have been confounding variables. The choice of catheter size can be influenced by the specificities of patients. For example, thinner catheters may be used for patients difficult to prick, such as cancer patients, who may have fragile veins.

In clinical practice, the indication of radiological examination determines the injection rate, which in turn defines the cannula size. Ultimately, the size may be limited by the fragility of the patient's veins. This generates two conclusions. First, professional expertise is important for assessing patients' venous capital. Second, the two variables, cannula size and injection rate, may not be independent and the relative weight of each of these variables in the outcome variations seems difficult to estimate without multivariate analyses. This kind of analyses was not performed in most of the selected articles. As statistics is part of the JBI critical appraisal checklist of the articles, care should be taken when interpreting these research results. Still, none of the studies that dealt with extravasation frequency found an influence of infusion rate, whether conducted on adults[23,26] or on children and adults.[40] Furthermore, in their study, Sinan et al.[23] separated the two variables when they investigated two infusion rates for each of two cannula sizes. An absence of significant effect of infusion rate on contrast extravasation was observed for the 18G and 20G catheters. New technological developments have led to the achievement of catheters usable with high injection rates.[37,45] These new needles (18G Fenestrated) were tested in 180 patients randomly allocated to three groups injected at flow rates that ranged from 5.4 mL/s to 8.3 mL/s (contrast medium: iopromide, Ultravist; Bayer Healthcare).[37] No extravasation was detected, and the diagnostic value was adequate. Most of the patients of the three groups did not show any discomfort, stress or pain.[37] Nonetheless, these results should be confirmed by a study involving more patients.

From a more general point of view, the use of a power injector did not seem to modify the extravasation rate significantly, in comparison with contrast material administration performed manually.[23]

The effect of venous access on extravasation frequency appeared to differ among the studies. In

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adults, Wienbeck et al.[26] found a higher rate of extravasation when the venous access was achieved using the hand rather than the antecubital fossa. However, another study in adults[19] and one in children found no effect. No data on extravasation frequency in cases of deep brachial IV cannulation were provided in the studies retained in this review. However, this could constitute a potential intervention, as suggested by Hardie and Kereshi.[46]

Rupp et al.[40] indicated that USGIV insertion may increase the risk of extravasation in comparison with a standard insertion. However, these results should be considered with caution because the patients in the two groups were not fully comparable. Although a multivariate logistic analysis was conducted, all confounding variables could not be considered. Thus, injections in both groups of patients may vary according to venous access or the size of the catheter used. Nevertheless, the USGIV allowed contrast medium injection in patients who possibly would not have had a contrast-enhanced CT scan because of the difficulty to prick them under the usual conditions.

Warming of two contrast products (Iopamidol 300 and 370) showed different results. Warming of iopamidol 370 decreased the extravasation frequency, whereas warming of iopamidol 300 had no effect.[27] It is interesting to note that once warmed, iopamidol 370 (viscosity of 20.9 cP at $20°C$ and 9.4 cP at $37°C$) is characterized by a viscosity similar to that of iopamidol 300 (viscosity of 8.8 cP at $20°C$ and 4.7 cP at $37°C$) at room temperature. This could explain the lower extravasation rate in these conditions. The warming of iopamidol 300 or 370, although supposed to fluidize the contrast material, was not found to increase the number of allergic-like reactions.[27] Despite these results, the authors stopped warming iopamidol 370 in their practice, citing as argument a lack of evidence and a stricter regulatory environment about warming of contrast media.

The extravasation rate did not seem to change according to the type of health professional performing the injection. Thus, irrespective of whether the professional was a staff from the radiology setting,[23] or the level of experience (medical students, staff radiologists, interns),[26] the extravasation rate was not significantly different between the groups. To confirm these results, one should ensure that the comparison groups were similar in all respects (health status, age, cannula caliber, etc.).

The implementation of a quality improvement program in 58 radiology settings in the United States reduced the rate of extravasation between pre- and post-implementation but not in a significant way.[32] However, data were collected by each of the institutions on a voluntary basis, without any on-site visits to check the veracity of the data or the implementation of the quality improvement program.

Three articles investigated the potential of EDA on extravasations.[38,39,41] The accessories detected extravasations, although two of the studies were mainly preliminary studies and did not provide sensitivity and specificity.[39,41] This information was only reported in the article of Birnbaum et al.[38] The device tested by these authors presented a sensitivity of 100% (95% CI: 51% – 100%), although the confidence interval was wide due to a low number of extravasations (4/500 injections). Its clinical validity therefore needs to be confirmed by further studies, particularly on a larger number of patients with existing catheters. This EDA requires less than 20 seconds to place it on the patient, which is a major advantage in a context where the patient flow rate for CT examinations is increasingly high. The device proposed by Saade et al.[41] takes more time to position, approximately three minutes, which might constitute an obstacle to its use in everyday practice. Hence, it may be more suitable to use it for patients with a more delicate venous access and at risk of extravasation. Furthermore, this article highlighted the fact that extravasation may occur during the test bolus phase.[41] In this context, an exploratory study[47] was conducted to detect injection errors (including extravasation) by using a saline injection test preceding acquisition.

Other technological innovations are being developed in this field, such as an EDA based on thermographic visualization.[48] After saline solution injection in the subcutaneous tissue of a volunteer's arm, the authors demonstrated the possibility of detecting extravasation by the subtraction of images recorded by the thermographic camera before and after the injection. This study was conducted on only one volunteer and by an induced extravasation with a saline solution instead of contrast media. It requires validation by further research, as is the case with the Nemoto extravasation sensor device.[49]

Volume of extravasate

Human characteristics such as patient gender and age were studied to determine whether they could constitute risk factors that affect extravasated volume.[28] These factors did not affect extravasated volume,[28] although gender seemed to have influenced extravasation rates.[26,42]

Several interventions to limit the extravasated volume were analyzed in the literature, among them the cannula gauge. This did not seem to have an effect.[28] Nonetheless higher extravasated volumes were documented for existing catheters versus freshly placed ones. These higher volumes may relate to lower pain sensation in persons with existing catheters, being generally inpatients or emergency patients, or to tissue injury leaving more room for extravasation.[28]

Furthermore, the infusion rate was shown to modify the volume of extravasation but in different ways depending on the studies. Wienbeck et al.[26] suggested a larger extravasated volume with an increased injection rate (from 1 to 8 mL/s). This could be explained as follows: with a higher administration rate, more liquid could extravasate during the period between the pain experienced by the patient and the interruption of the device by the operator. However, Moreno et al.[28] observed the opposite relationship, with injected rates ranging from 2 mL/s to 5 mL/s. The use of EDA was also tested for its effect on this outcome, and these accessories appeared to reduce the number of large volumes of extravasate.[32] These results are supported by observations made in another article.[38] Although the purpose of this article was not to estimate the extravasated volume with and without an EDA, the authors nevertheless reported the estimated volumes following the use of their system. It turned out that the reported volumes, between 13 and 18 mL, were substantially lower than the ones reported regularly in the literature (approximately 50–150 mL). Consequently, an EDA could reduce the extravasated volumes.

For this outcome Moreno et al.[28] also detected an effect of venous access. They obtained the largest volumes of extravasate when the administration occurred in the antecubital fossa and the smallest when in the hand. One hypothesis is that the tissues of the hands allows for little space, so that in case of extravasation, pain could be felt more quickly and therefore lead to a faster interruption of the injection. Finally, warming of two low-osmolality contrast materials did not modify the extravasation volume.[27]

An awareness project for healthcare professionals on extravasation was conducted in a multicenter study. However, the authors documented no decrease in the volume of extravasate after the campaign.[32]

The volume of extravasate is an important variable because it could play a role in the severity of injuries, that is, the larger the volume, the more serious the injury. This was demonstrated in two studies.[16,32] This was also confirmed by the results of a third study, although the trend in the latter was not statistically significant.[42] Therefore, strategies to reduce the volume extravasated and detect rapidly the extravasations become crucial. However, the practitioner must always remember that, as shown in these studies, serious damage can occur even with low extravasated volume.

Injury severity

Overall, the injury severity was not affected by the infusion rate. Wienbeck et al.[26] found the number of reactions to contrast material was similar between the three groups of infusion rates. Documented mild reactions included nausea, vomiting and hives; moderate reactions included shortness of breath; and severe reactions included irregular heartbeat. Similarly, Shaqdan et al.[42] found no difference in the distribution of injury severity, classified as mild, moderate or severe, in the three considered injection rates. The absence of a difference is expected. If the infusion rate affected injury severity, it certainly would have been a misleading relationship, originating from the relationship between the infusion rate and the volume extravasated. The implementation of a quality improvement project did not have an impact on the severity of the injury.[32] Furthermore, the frequency of plastic surgery consultations was the same for patients with USGIV insertion and those with standard insertion.[40]

Image quality

Image quality was rarely considered in the retrieved articles, despite this parameter being important, because it determined the diagnostic value. Only two studies examined this outcome. One of the studies indicated similar subjective image quality and aortic enhancement level for two types of

cannulas used (18G fenestrated and 20G non-fenestrated).[34] In another study, the Hounsfield units were not significantly different between the groups of patients who received injections at different injection rates.[37]

Limitations of the review

The searches performed in the databases were limited to articles published in English and French. Although only studies written in English were retained, articles published in other languages might have been missed. The quality of this systematic review directly depends on the primary articles on which it is based. As only two randomized trials were included and the other articles were observational studies, methodological biases in the primary studies could not be excluded. Furthermore, in the cohort studies, the effect of interventions was often tested with a statistical test for each variable. This engenders two problems. First, it increases the probability to have a significant statistical test result, just by chance. Second, the effect of the interventions or risk factors may be correlated, such as catheter size, infusion rate or patient age. As a consequence, multivariate statistical analyses would have been more appropriate. They would have allowed dissociation of the influence of interventions and an estimation of their respective weights (if any) on the outcome. Sample sizes were often small; without a power test, the absence of an intervention effect remains difficult to ascertain.

Conclusion

Our selection and evaluation processes of articles retained 15 studies. These studies investigated risk factors (e.g. patient demographics) and various interventions related to the physical features of the injection (e.g. cannula caliber and infusion rate), to a quality improvement project, or to devices for the extravasation detection. The outcomes investigated were extravasation frequency and volume, injury severity, and image quality. These articles suggested that injection rate, venous access and catheter dwell time could affect the volume extravasated. Regarding patient characteristics, being a woman may be a risk factor for extravasation, as well as being an inpatient or recently hospitalized. Preliminary studies seemed to indicate the potential of EDA to detect extravasation and to especially reduce the volume extravasated. With the other interventions, results

were either not significant or mixed across the studies. Given the quality of the primary studies (mild to moderate), the results should be interpreted with caution. However, this systematic review has a number of benefits. Firstly, it poses many suggestions to professionals who should always be vigilant about the risk of extravasation and its consequences. Secondly, it highlights the research gap in this area and the importance to pursue research with a solid methodological design.

Recommendations for practice

According to the JBI Grades of Recommendation, this systematic review has level B evidence. This applies to the effect of each intervention on each outcome. Level B means that the recommendations are ''weak''. This interpretation is based on the designs and analyses of the studies that have various methodological shortcomings. Nonetheless, given the rapid increase in the number of CT examinations, the extravasation frequency also increases. In this context, the personnel and the patient should be aware of extravasations to avoid them through appropriate strategies and detect them as soon as possible. Although little evidence exists about the risk factors of extravasation, age or patient specificity could be a risk factor. Hence, professionals should certainly be on alert when encountering such risk factors. Among the strategies that could contribute to the protection of patients against extravasations are the choice of the venous access, infusion rate, the insertion of a new catheter, and the use of extravasation detection accessories. The absence of significant results for the other strategies should not be considered as proof of their ineffectiveness. Owing to the small relative frequency of extravasation (although its absolute frequency is not rare), this event is cumbersome to study. Consequently, the clinical experience of health professionals should be an important component in decision-making.

Recommendations for research

Although several studies have been published on the prevention of extravasation risks, they are of mediocre quality, and the scientific evidence on this subject remains weak. Accordingly, this systematic review emphasizes the importance of conducting more research on extravasation prevention. This research should overcome the shortcomings reported in the existing articles, namely, selection bias,

confounding variables, or contrast material heterogeneity within studies. Multivariate statistical analyses would allow the dissociation of the effect of several variables and an estimation of their respective weights. Future research should estimate, before the start of a study, the appropriate sample size needed to detect an effect, or alternatively, after the experiment, determine the probability to detect an effect considering the sample size used. All the interventions considered in this review could be a subject for further research. Documentation of more than one outcome such as extravasation frequency, volume, injury severity and image quality is also pertinent. In the retrieved articles, the number of attempts to prick was considered as an outcome. This variable could also be considered as a potential risk factor of extravasation in new studies. Research to investigate the implementation of a quality project based on health professional training could be valuable. This would require a thorough follow-up of the implementation with an audit process. The technological innovations aimed at the detection of extravasations, revealed in this systematic review, are often either at the prototype stage or have only been tested on animals or on one or few human subjects. Clinical research with these new extravasation detection devices would be warranted. Estimations of their implications on patient workflow would also be necessary.

Acknowledgements

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Appendix I: Search strategy

PubMed (pubmed.gov): searched in September 2016

Search	Query
#1	"Contrast extravasation" OR (("Contrast Media"[Mesh] OR "contrast media" OR "contrast medium" OR "contrast agent" OR "contrast agents" OR "iodine" OR "iodinated contrast" OR "iodinated contrasts" OR "contrast material" OR "contrast materials") AND ("Extravasation of Diagnostic and Therapeutic Materials"[Mesh] OR extravasat*))
#2	"Tomography, X-Ray Computed"[Mesh] OR "computed tomography" OR "computed-tomography" OR "CT" OR "scanner" OR "CT-scan" OR "Computerised Tomography" OR "Computerized Tomography" OR "computer assisted tomography"
#3	#1 AND #2
Limit to ("1980/01/01"[PDat]: "2016/09/30"[PDat]) AND (English[lang] OR French[lang])	

CINAHL: searched in September 2016

Search	Query
#1	"Contrast extravasation" OR ((MH "Contrast Media+" OR "contrast media" OR "contrast medium" OR "contrast agent" OR "contrast agents" OR "iodine" OR "iodinated contrast" OR "iodinated contrasts" OR "contrast material" OR "contrast materials") AND (MH "Extravasation of Diagnostic and Therapeutic Materials" OR extravasat*))
#2	MH "Tomography, X-Ray Computed+" OR "computed tomography" OR "computed-tomography" OR "CT" OR "scanner" OR "CT-scan" OR "Computerised Tomography" OR "Computerized Tomography" OR "computer assisted tomography"
#3	#1 AND #2
Limit to January 1980-september 2016 + Exclude MEDLINE records	

Embase: searched in September 2016

Search	Query
#1	'contrast medium extravasation'/exp OR 'contrast medium extravasation' OR 'contrast extravasation'
#2	('contrast medium'/exp OR 'contrast medium' OR 'iodine' OR 'contrast media' OR 'contrast agent' OR 'contrast agents' OR 'contrast material' OR 'contrast materials' OR "contrast administration" OR "contrast infusion") AND ('extravasation'/exp OR 'extravasation' OR 'leakage' OR 'injection site extravasation'/exp OR 'injection site extravasation')
#3	#1 OR #2

(Continued)	
Search	**Query**
#4	'computer assisted tomography'/exp OR 'computer assisted tomography' OR 'computed tomography' OR 'computed-tomography' OR 'ct' OR 'scanner' OR 'ct-scan' OR 'computerised tomography' OR 'computerized tomography'
#5	#3 AND #4
Limit to ([english]/lim OR [french]/lim) NOT [medline]/lim AND [1980–2016]/py NOT [13–9–2016]/sd	

The Cochrane Register of Controlled Trials: searched in September 2016

Search	**Query**
#1	extravasation:ti,ab,kw
#2	MeSH descriptor: [Extravasation of Diagnostic and Therapeutic Materials] explode all trees
#3	#1 OR #2
#4	(pubmed or embase):an
#5	#3 NOT #4
Limit to: from 1980 to 2016	

Web of Science: searched in September 2016

Search	**Query**
#1	TOPIC: (contrast OR contrasts OR iodine)
#2	TOPIC: (extravasat* OR leakage)
#3	TOPIC: ("computed tomography" OR "computed-tomography" OR "ct" OR "scanner" OR "ct-scan" OR "computerised tomography" OR "computerized tomography" OR "computer assisted tomography")
#4	#1 AND #2 AND #3
Limit to: from 1980 to 2016 + LANGUAGES: (ENGLISH OR FRENCH) AND [excluding] Databases: (MEDLINE) AND Databases: (WOS)	

PsycINFO: searched in September 2016

Search	**Query**
#1	("computed tomography" or "computed-tomography" or "ct" or "scanner" or "ct-scan" or "computerised tomography" or "computerized tomography" or "computer assisted tomography").mp,hw or tomography/
#2	("extravasation" or "leakage").mp,hw
#3	("iodine" or "iod*" or "contrast" or "contrasts").mp,hw
#4	1 AND 2 AND 3
Limit to: (English or French) and yr="1980 - Current"	

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ProQuest Dissertations and Theses A&I: searched in September 2016

Search	Query
#1	all(contrast OR contrasts OR iod*)
#2	all(extravasat*)
#3	all(computed tomography OR computed-tomography OR ct OR scanner OR ct-scan OR computerised tomography OR computerized tomography OR computer assisted tomography)
#4	S1 AND S2 AND S3

TRIP Database: searched in September 2016

Search	Query
#1	radiology OR computed tomography
#2	extravasation
#3	"contrast medium" OR "contrast-media" OR iodine OR "contrast agent" OR "contrast agents" OR "contrast material" OR "contrast materials" OR "contrast administration" OR "contrast infusion"
#4	injection OR infusion
#5	#1 AND #2 AND #3 AND #4
Limit to: from:1980 to:2016	

ClinicalTrials.gov: searched in September 2016

Search	Query
#1	extravasation
#2	injection OR infusion OR intravenous
#3	#1 AND #2
Limit to: received on or after 01/01/1980 | updated on or before 12/09/2016	

Appendix II: Excluded studies

Abe S, Mizuno N, Tani S, Nishikawa M, Yabunaka K, Mizuta M, Katsuda T, Sanada S. Effectiveness of the new injection program ''saline test injection mode'' for use of a power injector in pediatric contrast CT
Reason for exclusion: No comparison between interventions reducing risk of extravasation.

Alami Z, Nasri S, Ahid S, Kacem HH. Extravasation of contrast medium during CT examination: an observational case-control study
Reason for exclusion: The characteristics of the control and extravasation groups appear to be different. Additionally, the statistical analyses not clearly described in the paper.

Bouton CE, Lombardi T, Hobson FR, Stark G. Experimental detection of subcutaneous contrast extravasation using radio frequency permittivity sensing
Reason for exclusion: Case series provoking extravasation with fluid.

Callahan MJ, Servaes S, Lee EY, Towbin AJ, Westra SJ, Frush DP. Practice patterns for the use of iodinated i.v. contrast media for pediatric CT studies: a survey of the Society for Pediatric Radiology
Reason for exclusion: This article is a survey and does not evaluate interventions.

Cochran ST, Bomyea K, Kahn M. Treatment of iodinated contrast material extravasation with hyaluronidase
Reason for exclusion: Several different methods of venous access are combined in this study, including a Port-a-cath which is not considered in our review.

Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media
Reason for exclusion: No interventions causing a reduction in extravasation are compared.

Cohan RH, Bullard MA, Ellis JH, Jan SC, Francis IR, Garner WL, Dunnick R. Local reactions after injection of iodinated contrast material
Reason for exclusion: Investigation includes venography and urography in addition to CT.

Federle MP, Chang PJ, Confer S, Ozgun B. Frequency and effects of extravasation of ionic and non-ionic CT contrast media during rapid bolus injection
Reason for exclusion: Problem of consistency between the data and the statistical analyses.

Grant KL, Camano JM. Adverse events and cost savings three years after implementation of guidelines for outpatient contrast-agent use
Reason for exclusion: Patients in the two groups (LOCM vs. HOCM) are dissimilar and may present different extravasation risks.

Hardie AD, Kereshi B. Incidence of intravenous contrast extravasation: increased risk for patients with deep brachial catheter placement from the emergency department
Reason for exclusion: The data are rough approximations.

Hollot B, Bullano KH. Ethnographic research of IV contrast agent in hospital CT scanning suites.
Reason for exclusion: The study is qualitative and interventions are not evaluated.

Jacobs JE, Birnbaum BA, Langlotz CP. Contrast media reactions and extravasation: relationship to intravenous injection rates
Reason for exclusion: Cohort study with too many confounding variables.

Juchem BC, Dall'Agnol CM. Immediate adverse reactions to intravenous iodinated contrast media in computed tomography

Reason for exclusion: The methodology is not described clearly enough and important confounding factors are potentially present.

Kadom N, Hashim HD, Olsen C, Cefaratti M, Bulas D, Shalaby-Rana E. Nursing role model for computed tomography contrast injection decreases extravasation rates
Reason for exclusion: The relative frequencies of extravasation per intervention are not provided.

Kaste SC, Young CW. Safe use of power injectors with central and peripheral venous access devices for pediatric CT
Reason for exclusion: The relative frequencies of extravasation per intervention are not provided.

Kingston RJ, Young N, Sindhusake DP, Truong M. Study of patients with intravenous contrast extravasation on CT studies, with radiology staff and ward staff cannulations
Reason for exclusion: The relative frequencies of extravasation per intervention are not provided. For the only variable that could be used in this systematic review (the location of cannulation), the statistical results do not seem in accordance with the raw data provided.

Lee YH, Chen CCC, Lee SK, Chen CY, Wan YL, Guo WY, Cheng A, Chan WP. Patient safety during radiological examinations: a nationwide survey of residency training hospitals in Taiwan.
Reason for exclusion: The relative frequencies of extravasation per intervention are not provided.

Mihl C, Kok M, Wildberger JE, Turek J, Muehlenbruck G, Das M. Computed tomography angiography with high flow rates. An in vitro and in vivo feasibility study
Reason for exclusion: No interventions causing a reduction in extravasation are compared.

Miles SG, Rasmussen JF, Litwiller T, Osik A. Safe use of an intravenous power injector for CT: experience and protocol
Reason for exclusion: There is no comparison group.

Mossard J, Gomersall JS. Prevention of extravasation of intravenous computerised tomography contrast media among adult patients in the medical imaging department of an acute tertiary hospital: A best practice implementation project
Reason for exclusion: This paper is an audit of practice. The relative frequencies of extravasation per intervention are not provided.

Nakamura K, Sasaki T, Ohga S, Yoshitake T, Terashima K, Asai K, Matsumoto K, Shinoto M, Shioyama Y, Nishie A, Honda H. Thermographic visualization of the superficial vein and extravasation using the temperature gradient produced by the injected materials
Reason for exclusion: Saline solution rather than contrast medium is used in this study.

Nelson RC, Anderson FA, Birnbaum BA, Chezmar JL, Glick SN. Contrast media extravasation during dynamic CT: detection with an extravasation detection accessory
Reason for exclusion: This paper introduces a detection accessory. This device is thoroughly tested in a later article published by the same authors.

Powell CC, Li JM, Rodino L, Anderson FA. A new device to limit extravasation during contrast-enhanced CT
Reason for exclusion: Equivalents of contrast media were used.

Sbitany H, Koltz PF, Mays C, Girotto JA, Langstein HN. CT contrast extravasation in the upper extremity: strategies for management
Reason for exclusion: The links between the interventions and the outcome are not evaluated in the article.

Shuman WP, Adam JL, Schoenecker SA, Tazioli PR, Moss AA. Use of power injector during dynamic computed tomography

Reason for exclusion: There is no comparison group.

Sistrom CL, Gay SB, Peffley L. Extravasation of iopamidol and iohexol during contrast-enhanced CT: Report of 28 cases
Reason for exclusion: There are too many identified confounding variables. Additionally, injection rates are very low compared to the actual practice.

Teo MSK, Ong CMLC, Ying SSA. Extravasation of contrast medium during CT scanning-tracking and reduction of rate of extravasation.
Reason for exclusion: It is not an intervention test but a quality improvement project with many factors.

Tonolini M. Contrast Medium Extravasation: The Importance of Radiographic Assessment.
Reason for exclusion: The article focuses on the assessment of contrast media extravasation and not prevention.

Wang CL, Cohan RH, Ellis JH, Adusumilli S, Dunnick NR. Frequency, management, and outcome of extravasation of nonionic iodinated contrast medium in 69,657 intravenous injections.
Reason for exclusion: The relative frequencies of extravasation per intervention are not provided.

Yellen M. Reducing IV infiltration with administration of IV contrast
Reason for exclusion: It is not an intervention test but a quality improvement project with many factors.

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Appendix III: List of included studies

Study	Methods	N	Participants	Variables considered in the study	Contrast media	Outcomes	Extravasation rate
Amaral et al. (2006)[9]	Prospective cohort study	557 injections	Children	- Injection site - Gauge	Iohexol: Omnipaque 300 (Nycomed)	Extravasation frequency	0.36%
Birnbaum et al. (1999)[38]	Case series	500 injections	Adults	EDA	- Omnipaque 300 (Nycomed) - Isovue 300 (Bristol-Myers) - Conray 60 (Mallinckrodt Medical) - Hypaque 60 (Nycomed)	Detection of extravasation (sensitivity and specificity)	0.8%
Davenport et al. (2012)[27]	Retrospective cohort study	24820 injections	Adults and children	Warming of CM	- Iopamidol 300: Isovue (Bracco Diagnostics) - Iopamidol 370: Isovue (Bracco Diagnostics)	Extravasation frequency Volume of extravasate	0.23−0.87%
Dykes et al. (2015)[32]	Pre-/post-intervention study	454497 injections	Adults and children	1−2−3. Practice quality improvement 2. EDA	No information provided	1. Extravasation frequency 2. Volume of extravasate 3. Injury severity	0.24%
Hoff et al. (2008)[39]	Case series	198 injections	Adults	EDA	No information provided	Detection of extravasation	0.5%
Johnson et al. (2014)[36]	Pseudo-randomized trial	205 injections	Adults	Gauge	No information provided	- Extravasation frequency - Subjective image quality - Aortic enhancement level	0%
Johnson et al. (2014)[34]	Prospective cohort study	1000 injections	Adults	Patient specificity	- Iodixanol: Visipaque 320 (GE Healthcare) - Iohexol: Omnipaque 350 (GE Healthcare)	Extravasation frequency	0.4−0.8%
Kok et al. (2016)[37]	Randomized control trial	180 injections	Adults	Contrast media concentration and flow rates	Ultravist 240, 300, 370 mg I/mL, iopromide (Bayer Healthcare)	- Extravasation frequency - Enhancement level	0%
Moreno et al. (2013)[28]	Retrospective cohort study	330 extravasations	Adults	- Infusion rate - Injection site - Gauge - Catheter dwell time - Patient sex - Patient age	No information provided	Volume of extravasate	0.3%
Rupp et al.(2016)[40]	Retrospective cohort study	40143 injections	Adults	Contrast administration (USGIV insertion vs standard IV)	No information provided	Extravasation frequency	- 3.6% with USGIV insertion - 0.3% with standard IV
Saade and Brennan (2011)[41]	Case series	25 injections	Adults at high risk of contrast extravasation	EDA	Iopromide 370	Extravasation detection	0.2%
Schwab et al. (2009)[19]	Quasi-experimental study	58 injected patients with the standard CT protocol	Adults	- Injection site - Gauge (20G vs 22G) - Infusion rate (3mL/sec vs 5mL/s)	Iopamidol: Solustrat 300® (Bracco-Altana Pharma GmbH)	Extravasation frequency	0−7.7%

(Continued)							
Study	Methods	N	Participants	Variables considered in the study	Contrast media	Outcomes	Extravasation rate
Shaqdan et al. (2014)[42]	Retrospective cohort study	352125 injections for CT examination	Adults and children	1–2. Infusion rate 1. Patient sex 1. Patient age 1. Patient specificity	Iopamidol: Isovue 370 (Bracco Diagnostics)	1. Extravasation frequency 2. Injury severity	0.13%
Sinan et al. (2005)[23]	Prospective cohort study	2640 injections with power injector	Adults	- Gauge (18G vs 20G) - Infusion rate - Professional injecting	- Ultravist 300 - Omnipaque 240 - Omnipaque 300	Extravasation frequency	0.3%
Wienbeck et al. (2010)[26]	Retrospective cohort study	4457 injections	Adults	1–2–3. Infusion rate 1. Injection site 1. Gauge (16–24G) 1. Professional injecting 1. Patient sex 1. Patient age	- Iopromide: Ultravist 300 & Ultravist 370 (Bayer Schering Pharma) - Iomeprol: Iomeron 300 & Iomeron 350 (Bracco Altana Pharma)	1. Extravasation frequency 2. Volume of extravasate 3. Injury severity	1.2%

CM, Contrast media; EDA, Extravasation Detection Accessory; G, Gauge; USGIV, Ultrasound-guided intravenous catheter.