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TITLE

Risk factors for difficult peripheral venous cannulation in hospitalised patients. A multicentre case-control study protocol

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ABSTRACT

Introduction. Patients with difficult venous access experience undesirable effects during health care, such as delayed diagnosis and initiation of treatment, stress and pain related to the technique, and reduced satisfaction. This study aims to identify risk factors with which to model the appearance of difficulty in achieving peripheral venous puncture in hospital treatment.

Methods and analysis. Case-control study (). We will include adult patients requiring peripheral venous cannulation in eight public hospitals, excluding those in emergency situations and women in childbirth or during puerperium. The nurse who performs the technique will record in an anonymised register variables related to the intervention. Subsequently, a researcher will extract the health variables from the patient's medical history. Patients who present one of the following conditions will be assigned to the case group: two or more failed punctures, need for puncture support, need for central access after failure to achieve peripheral access, or decision to reject the technique. The control group will be obtained from records of patients who do not meet the above conditions.

A descriptive analysis will be made of the distribution of the phenomenon. The variables hypothesised to be risk factors for the appearance of difficult venous cannulation will be studied using a logistic regression model.

Ethics and dissemination. The study was funded on January 2017 and obtained ethical approval by the Research Ethics Committee of the Balearic Islands. Informed consent will be obtained previous to data collection. Results will be published in a peer-reviewed scientific journal.

Discussion. The study will establish a profile of patients at risk, by means of which nurses can identify patients in this situation at an early stage, thus facilitating the timely and selective use of puncture support methods such as ultrasound or infrared.

STRENGHTS ANS LIMITATIONS OF THIS STUDY

- To our knowledge, no previous case-control studies have been conducted to identify risk factors for difficult peripheral cannulation, or to describe this problem in different health care settings.
- Profiles of patients at risk are needed in order to improve decision-making regarding cannulation routes and techniques, and to ensure the suitability and maintenance of different devices.
- Furthermore, no previous studies have examined this event in different care settings. Such an approach is needed because the user profile and the care setting could influence the occurrence of cannulation difficulty.

INTRODUCTION

Peripheral venous catheters (PVCs) are the most commonly used invasive devices in hospital care (1). Although the insertion of a PVC is usually a simple technique, difficulty can arise in this cannulation, requiring multiple punctures before the device is correctly situated. Multiple puncture provokes delays in care, in obtaining diagnosis or in initiating treatment (2–4). Furthermore, it generates stress, heightens perceptions of pain (Fields et al., 2014) and reduces satisfaction, both among patients and among the professionals performing the technique (4,5).

In addition, multiple puncture may be associated with a progressive deterioration of the vascular tree, termed “vascular exhaustion”, which makes vascular access even more difficult in successive contacts with the patient (6).

Background

Although difficult peripheral intravenous cannulation (DPIVC) occurs in 10-24% of adults and in up to 37% of children who require a peripheral route during hospital treatment, in many respects it is still insufficiently studied (4). Although there is no consensus among researchers as to the necessary conditions for considering a case as “difficult”, DPIVC is generally understood as arising when two or more punctures are performed without success, or when puncture support methods are required, or when the impossibility of obtaining peripheral access means that a central venous catheter (CVC) must be inserted (7). Most current research in this area addresses the development of puncture support techniques (2), especially ultrasound, and few studies have analysed DPIVC as a health problem, or the factors that may promote its appearance.

DPIVC is associated with a greater need for CVC, and studies have shown that a high percentage of the latter catheters are inserted not because of the patient’s therapeutic needs but because it is impossible to use a peripheral access catheter (8). This circumstance heightens both the number and the severity of complications associated with catheter access, such as local infection, bacteraemia, thrombosis and pneumothorax. These, and other complications, are in turn associated with increased duration of hospital stay, greater morbimortality and higher costs (8–10).

Significant health benefits could be achieved by avoiding potentially unnecessary central catheters (11). For example, regarding bacteraemia related to venous catheterisation, which is the principal and most severe complication in this respect, the

incidence is significantly higher for central catheters; thus, bacteraemia affects 2.7 cases per 1,000 days of central catheterisation, but only 1.1 cases per 1000 days of peripheral intravenous central catheter (PICC) and 0.5 cases per 1,000 days for peripheral access (9,12). Indeed, venous catheter-related bacteraemia may be considered an independent cause of hospital morbidity and mortality, as each case generates an additional 10-20 days of hospital stay and increases costs by between $4,000 and $56,000 (13).

In fact, in many cases, CVCs are inserted unnecessarily. Studies have reported a reduction of 80-85% in the use of CVC in hospital patients with DPIVC when specific programmes were implemented (8). Similarly, Stokowski et al. in 2009 (10) observed a marked reduction in PICC-related complications (bacteraemia, thrombosis, obstruction and accidental withdrawal) following the provision of a training programme for nurses in the use of ultrasound techniques for venous cannulation. Implementation of this programme also reduced variability among other health professionals involved (radiologists, surgeons and anaesthetists), producing cost savings of 270-305 Canadian dollars for each catheter inserted. A similar programme, conducted in Texas, USA, achieved a 74% reduction in the number of CVCs inserted (including intensive care), mainly by replacing them with PICCs, which were inserted by nurses trained in the use of ultrasound techniques (14). This intervention reduced costs by $200,000 per year, or $1,614 per PICC inserted.

Risk factors for difficult peripheral intravenous cannulation

It has been argued that strategies should be promoted to avoid multiple puncture and the undesirable effects of central access catheterisation (15). Although there is a growing body of evidence in favour of cannulation support methods (ultrasound, infrared and transillumination), few studies have attempted to identify risk factors for DPIVC or the profiles of patients likely to present it. To our knowledge, the only studies conducted in this area, to date, have been limited to specific hospital areas (intensive care, A&E, paediatrics and oncology), and so there is little scope for comparing different approaches. Specifically, it has been suggested that several advanced chronic conditions may contribute to the progressive degradation of the peripheral vascular tree, such as obesity, vasculopathy and chronic pluripathology (6,16–19). However, these studies focus on the application of ultrasound to improve the effectiveness of puncture techniques, and so their approach to potential risk factors should be considered with caution.

In the context of hospital A&E services, three earlier studies have made interesting findings.

Sebbane et al. conducted a study in France in 2013, without a control group, evaluating risk factors that determine the success of the first attempt at cannulation (20). These authors observed an association between extreme values for body mass index and the appearance of DPIVC, which was also associated with poor assessment by the health professional (whether doctor or nurse) of the viability of access. In fact, the professional's view of the feasibility of cannulation has been explored in various studies, many of which have found it to be a relevant factor and a possible predictor of difficulty in obtaining venous access (21). Another study concluded that certain variables related to the professional who performs the technique, regarding his/her professional experience in general and concerning venous cannulation in particular, may also influence the effectiveness of the intervention (22).

In 2016, Carr et al. performed a cohort study which sought to identify factors relevant to the success of venous cannulation in patients treated at hospital A&E units (23). These authors, too, highlighted the importance of the professional's assessment of the viability of venous access (visibility and palpability of the vein), in addition to factors such as cachexia (wasting syndrome) and advanced age, which were potentially associated with difficulty. This study also identified differences related to the location of the vein to be punctured and to the cannulation experience of the clinician performing the technique.

Finally, Fields et al. reported that previous pathological conditions, such as diabetes, parenteral drug abuse and spindle cell disease, can increase the risk of DPIVC (24). Other relevant factors, although to a lesser extent, were previous episodes of puncture difficulty and the need for puncture support systems, observed in previous contacts with the patient.

In view of this background, we consider it necessary to analyse, in a single study, the different variables that have been proposed as potential risk factors for difficulty in cannulation, including care settings other than hospital A&E units.

In this project, we aim to identify the risk factors affecting patients with DPIVC, and to determine the weight of each of these factors, so that a model can be established by means of which patients at risk can be identified at an early stage and so that puncture

support methods can be prioritised (25), taking into account that the use of such methods is increasingly recommended (26).

METHODOLOGY

Hypothesis

There exist risk factors that can be identified and used to generate a profile of hospital patients with difficult peripheral intravenous cannulation.

Aims

The main study goal is to identify the possible risk factors associated with the patient, thus enabling us to establish a model with which to estimate the probability of difficult access to venous cannulation in hospital treatment.

Secondary goals:

- To determine the characteristics of patients with DPIVC according to different care profiles (medical hospitalisation, surgical hospitalisation, surgical area and A&E-intensive care).
- To describe the type of venous catheter insertion technique according to the appearance of difficulty in cannulation: number of punctures required, perception of pain, resources needed (number of professionals and estimated time required) and need for alternative methods (CVC, ultrasound support, referral to other professionals).
- To determine whether the occurrence of such difficulty is influenced by the experience and characteristics of the health professional involved.

Methods and analysis

Design. Case-control study with incident cases.

Settings. 48 units, corresponding to different care settings: A&E, intensive care, surgical area and hospitalisation units, in eight public hospitals in the Spanish National Health System, with diverse profiles, including three university hospitals and five second-level hospitals.

Subjects. Adults for whom peripheral pathway cannulation is performed or attempted, and who consent to participate in the study. Patients in emergency situations and women during childbirth or puerperium will be excluded.

Data collection. The nurse who performs the technique will record, in an anonymised record, the variables related to the intervention and the patient's medical history number. All nurses may add such records during the study period. Members of the research team will retrospectively review the medical history to compile the health variables. The data collection system was piloted in four of the above hospital units in February 2016.

All patients in the sample population who present DPIVC at some time will be included in the case group if they meet at least one of the following conditions: two or more failed punctures; the need for puncture support techniques (ultrasound, infrared or transillumination) when accessible vessels cannot be identified (excluding ultrasound scans for other purposes); the need for central access after failure to achieve peripheral access or decision not to implement it (no venous access achieved and the procedure is abandoned). Subsequently, we will determine the distribution of the incidence of DPIVC by hospital environments (medical hospitalisation units, surgical hospitalisation units, surgical area and A&E-intensive care). To offset the effects of possible differences in the inclusion of patients and their different profiles according to the units participating in the study, the control group will be selected by random sampling stratified by the same treatment environments, following the distribution of incidence observed in the case group. This sample will be composed of the patients included in the study who do not present the conditions for selection to the case group. Three controls will be selected for each case. The nurses will be blinded to the selection criteria for cases and controls, in order to avoid selection bias.

Since the study will require the involvement of a significant number of professionals from different environments, a team of collaborators has been recruited to coordinate the study in their respective units and centres, thus serving as a bridge between the research team and the other professionals.

Variables and definitions. Taking into account previous studies in this field, 13 variables will be hypothesised as possible risk factors. Variables will also be considered to assess the comparability of the case and control groups. Table 1 lists these variables and their definitions.

Sample. The minimum sample size was calculated taking as a reference the risk factor "diabetes" from the study of A&E patients conducted by Fields et al. in 2014 (24). Assuming an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral test, we calculated that 87 cases and 261 controls would be required to detect a minimum odds ratio of 2.1, assuming a rate of exposure of 0.5 in the control group. In this consideration, the Poisson method was used. In addition, another ten cases were attributed by category, following the system described by Peduzzi et al. (27), and so the total minimum sample required is 207 cases. Assuming a frequency of 10%, 2070 patients must be identified to achieve the population size required for the case group. The estimated time to reach this sample size is ten months, although this could be extended if necessary.

Data analysis. A descriptive analysis of the variables will be performed, including the distribution of the phenomenon by hospital environments and services (type of attention). Tests of association will be applied between the main study variables: hypothetical risk factors, characteristics of the technique, environment, and experience of the professional. The association will be determined by bivariate analysis based on chi-square, Student's t, Mann-Whitney U, Wilcoxon W and Friedman tests, ANOVA and Pearson and Spearman correlations, depending on the nature and normality of distribution of the variables. Subsequently, the variables hypothesised as risk factors for the onset of DPIVC will be analysed using a logistic regression model, to obtain the respective adjusted odds ratios.

Validity and reliability / Rigour

The fact that cases and controls will be recruited from the same source, together with the inclusion of sample adjustment variables, will ensure the reliable comparability of the groups.

The control group will be distributed by stratified random sampling, which will ensure the homogeneity of the case and control groups.

Blinding to the study hypothesis and to the variables hypothesised as risk factors will prevent any selection bias that might arise in the nurses participating in the data collection process.

Relevant variables will be considered in order to study the possible influence of the professional profile of the nurse performing the technique on the appearance of DPIVC.

The multicentre nature of the study and the inclusion of different hospital profiles, and of hospitals located in different geographic areas, will enhance the diversity of the sample and its external validity.

Limitations

The variable “spindle cell disease” is not included in our study because of its low prevalence in the reference population. Since our study focuses on patient risk factors, variables related to the nurse’s experience have not been hypothesised as potential risk factors. An association analysis of these variables will be conducted to determine whether future studies in this regard are needed.

Ethics and dissemination

The study does not involve intervention or change in usual practice. The patients will be asked to give their signed informed consent, and will be provided with clearly-written information about the purpose and implications of the research.

The computerised database does not contain patient identification. The individuals involved in compiling data will sign a confidentiality agreement.

The project has been peer evaluated and approved by the reference Research Ethics Committee (code IB3137/16PI) and by the research committees of each of the participating centres.

The results of this study will be sent to a peer-reviewed scientific journal for publication.

CONCLUSIONS

The proposed study will enable us to obtain profiles of patients at risk of difficulty in peripheral venous cannulation. Identifying this risk at an early stage will facilitate the early and selective use of puncture support methods such as ultrasound or infrared imaging.

Nurse-led intravenous treatment teams can use this information to identify priority patients and to ensure the appropriateness of the interventions made. The information obtained regarding the use of nursing resources for managing DPIVC may also be useful for these teams.

AUTHOR CONTRIBUTIONS

All authors have agreed on the final version and meet both of the following criteria [recommended by the ICMJE (http://www.icmje.org/ethical_1author.html)]:

- substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content.

MARC coordinates the research team and is responsible for reporting Ethic Committees and every institution involved in the study . MARC and IBM revised previous literature about puncture difficulty in adults, and designed data collection methods along with LJMB, IFF, CMM and LMM. JEPG and JMMA audited the study design, especially concerning statistical analysis proposed. IFF designed and maintains the database to ensure data validity. MARC, IBM, JEPG and JMMA wrote first version of the protocol, which was later edited by all the authors.

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COPETING INTERESTS STATEMENT

The authors have no conflict of interest to declare.

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TABLE 1. Variables and definitions

VARIABLE	DEFINITION
Variables analysed to assess the comparability of groups:	
Age (continuous quantitative variable)	
Sex	
Specialist area	Hospital area where treatment is provided.
Reason for admission	Main diagnosis on admission; pathologies grouped by diagnostic group according to the International Classification of Diseases.
Variables regarding the cannulation technique:	
Arterial blood pressure before cannulation	
Number of punctures made	
Catheter inserted (yes/no)	
Calibre of catheter inserted	
RN	Number of nurses participating.
NA	Number of nursing assistants participating.
Time	Estimated time, in minutes, spent implementing the technique, by all professionals.
Pain intensity after implementation of the technique	Evaluation of pain perceived by the patient after cannulation, measured on a Visual Analogue Scale.
Need for alternative methods or techniques: • Central venous catheter • Ultrasound, infrared or transillumination • Referral to other professionals or hospital services • Access via lower limbs or other alternative locations.	

Rejection of cannulation, in favour of: • Oral route. • Subcutaneous route. • Nasogastric tube. • Central venous catheter. • Other.	
Variables hypothesised as risk factors for DPIVC:	
Age (4 categories)	
Non-palpable vein	Vein not palpable, in the opinion of the nurse performing the technique.
Non-visible vein	Vein not visible, in the opinion of the nurse performing the technique.
History of DPIVC	Known history of DPIVC. Evidence in the patient's medical history of difficulty in obtaining a venous route, or the patient describes such a difficulty in a previous experience.
Upper-limb alterations	Visible alterations in the upper extremities: oedema, haematoma, inflammation, surgical interventions, medical devices or any other circumstance that hinders or limits the puncture. If any such alteration is present, we will distinguish between acute alterations (less than three months from appearance) and chronic or permanent alterations (qualitative variable with three categories).
Previous punctures	Punctures carried out before the present episode. During the present treatment episode, a venous catheter has previously been inserted (or insertion has been attempted).
Previous episodes	Hospitalisation or A&E attention during the last 90 days.
Diabetes mellitus	
Parenteral drug abuse	Documented history or current use of parenteral drugs.

Chemotherapy	Chemotherapy now or during the last 90 days.
BMI	Body mass index. Only extreme values have been associated with DVIPC, and so this parameter will be compiled as a qualitative variable, with three categories: <18.5; 18.5-30; >30.
HD	Haemodialysis programme. Documented history or current use of a long-term programme of haemodialysis.
COPD	Chronic obstructive pulmonary disease.
Variables related to the nurse performing the cannulation technique:	
Experience (years)	Years of nursing experience.
Technique (years)	Years of experience in peripheral venous cannulation. Number of years during which the nurse has worked in settings where peripheral venous cannulation is regularly performed.
Age	
Sex	

Risk factors for difficult peripheral venous cannulation in hospitalised patients. A multicentre case-control study protocol

Miguel Angel RODRIGUEZ-CALERO et al.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	*(a) Indicate the study's design with a commonly used term in the title or the abstract* Both title (page 1) and abstract (page 2) contain explicit information about case-control design
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found The abstract includes information about methods and data collection, statistical analyses intended to be done, as well as potential utility of results.
Introduction		
Background/rationale	2	*Explain the scientific background and rationale for the investigation being reported* Pages 4 and 5 offer information about previous studies addressing venous access in general, and difficult peripheral venous access in particular. In pages 5 and 6, we present previous studies about potential risk factors and gaps to be covered with our research.
Objectives	3	*State specific objectives, including any prespecified hypotheses* Page 7: conceptual hypothesis and aims.
Methods		
Study design	4	*Present key elements of study design early in the paper* Page 7
Setting	5	*Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection* Pages 7-8. Description of settings (48 units of 8 public hospitals) and the processes of data collection.
Participants	6	*(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls* In page 8 we describe subjects and inclusion/exclusion criteria.
		(b) For matched studies, give matching criteria and the number of controls per case
Variables	7	*Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable* Page 8: 'Variables and definitions'. Table 1 offers further information about every variable included in the study.
Data sources/ measurement	8*	*For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment*

		methods if there is more than one group Page 8 (variables) and Table 1.
Bias	9	*Describe any efforts to address potential sources of bias* In page 9 ('Validity and reliability / rigour') we describe efforts to reduce risk of bias, especially regarding data collection and comparability of groups.
Study size	10	*Explain how the study size was arrived at* Sample size and number of controls per case are described in page 9, 'sample'.
Quantitative variables	11	*Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why*
Statistical methods	12	*(a) Describe all statistical methods, including those used to control for confounding* Statistical methods are described in page 9, 'Data analysis'. Some variables regarding professional expertise of the nurse are used as potentially confounding factors.
		(b) Describe any methods used to examine subgroups and interactions Page 9, 'Data analysis'. This study will explore the distribution of venous cannulation difficulty in different environments (settings), which has never been explored in a single study.
		(c) Explain how missing data were addressed
		(d) If applicable, explain how matching of cases and controls was addressed
		(e) Describe any sensitivity analyses
Results *(not applicable in protocol reporting)*		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	*Summarise key results with reference to study objectives*
Limitations	19	*Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias* Limitations are described in page 10
Interpretation	20	*Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence* As there are not available results to be discussed, we include in 'Conclusions' (page 10) some aspects regarding the utility of our investigation and data applicability.
Generalisability	21	*Discuss the generalisability (external validity) of the study results*
Other information		
Funding	22	*Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based* Page 11, funding statement

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Risk factors for difficult peripheral venous cannulation in hospitalised patients. Protocol for a multicentre case-control study in forty-eight units of eight public hospitals in Spain

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TITLE

Risk factors for difficult peripheral venous cannulation in hospitalised patients. Protocol for a multicentre case-control study in forty-eight units of eight public hospitals in Spain

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ABSTRACT

Introduction. Patients with difficult venous access experience undesirable effects during health care, such as delayed diagnosis and initiation of treatment, stress and pain related to the technique, and reduced satisfaction. This study aims to identify risk factors with which to model the appearance of difficulty in achieving peripheral venous puncture in hospital treatment.

Methods and analysis. Case-control study. We will include adult patients requiring peripheral venous cannulation in eight public hospitals, excluding those in emergency situations and women in childbirth or during puerperium. The nurse who performs the technique will record in an anonymised register variables related to the intervention. Subsequently, a researcher will extract the health variables from the patient's medical history. Patients who present one of the following conditions will be assigned to the case group: two or more failed punctures, need for puncture support, need for central access after failure to achieve peripheral access, or decision to reject the technique. The control group will be obtained from records of patients who do not meet the above conditions. It has been stated a minimum sample size of 2070 patients, 207 cases and 1863 controls.

A descriptive analysis will be made of the distribution of the phenomenon. The variables hypothesised to be risk factors for the appearance of difficult venous cannulation will be studied using a logistic regression model.

Ethics and dissemination. The study was funded on January 2017 and obtained ethical approval by the Research Ethics Committee of the Balearic Islands. Informed consent will be obtained previous to data collection. Results will be published in a peer-reviewed scientific journal.

STRENGHTS ANS LIMITATIONS OF THIS STUDY

- To our knowledge, no previous case-control studies have been conducted to identify risk factors for difficult peripheral cannulation, or to describe this problem in different health care settings.
- Cases and controls will be reported by clinicians using the same source and of recordings. Blinding study hypothesis and criteria for the assignment to each group, will ensure a reliable comparability.
- Profiles of patients at risk are needed in order to improve decision-making regarding cannulation routes and techniques, and to ensure the suitability and maintenance of different devices.

INTRODUCTION

Peripheral venous catheters (PVCs) are the most commonly used invasive devices in hospital care (1). Although the insertion of a PVC is usually a simple technique, difficulty can arise in this cannulation, requiring multiple punctures before the device is correctly situated. Multiple puncture provokes delays in care, in obtaining diagnosis or in initiating treatment (2–4). Furthermore, it generates stress, heightens perceptions of pain (5) and reduces satisfaction, both among patients and among the professionals performing the technique (4,6).

In addition, multiple puncture may be associated with a progressive deterioration of the vascular tree, termed “vascular exhaustion”, which makes vascular access even more difficult in successive contacts with the patient (7).

Background

Although difficult peripheral intravenous cannulation (DPIVC) occurs in 10-24% of adults and in up to 37% of children who require a peripheral route during hospital treatment, in many respects it is still insufficiently studied (4). Although there is no consensus among researchers as to the necessary conditions for considering a case as “difficult”, DPIVC is generally understood as arising when two or more punctures are performed without success, or when puncture support methods are required, or when the impossibility of obtaining peripheral access means that a central venous catheter (CVC) must be inserted (8). Most current research in this area addresses the development of puncture support techniques (2), especially ultrasound, and few studies have analysed DPIVC as a health problem, or the factors that may promote its appearance.

DPIVC is associated with a greater need for CVC, and studies have shown that a high percentage of the latter catheters are inserted not because of the patient’s therapeutic needs but because it is impossible to use a peripheral access catheter (9). This circumstance heightens both the number and the severity of complications associated with catheter access, such as local infection, bacteraemia, thrombosis and pneumothorax. These, and other complications, are in turn associated with increased duration of hospital stay, greater morbimortality and higher costs (9–11).

Significant health benefits could be achieved by avoiding potentially unnecessary central catheters (12). For example, regarding bacteraemia related to venous catheterisation, which is the principal and most severe complication in this respect, the

incidence is significantly higher for central catheters; thus, bacteraemia affects 2.7 cases per 1,000 days of central catheterisation, but only 1.1 cases per 1000 days of peripheral intravenous central catheter (PICC) and 0.5 cases per 1,000 days for peripheral access (10,13). Indeed, venous catheter-related bacteraemia may be considered an independent cause of hospital morbidity and mortality, as each case generates an additional 10-20 days of hospital stay and increases costs by between $4,000 and $56,000 (14).

In fact, in many cases, CVCs are inserted unnecessarily. Studies have reported a reduction of 80-85% in the use of CVC in hospital patients with DPIVC when specific programmes were implemented (9). Similarly, Stokowski et al. in 2009 (11) observed a marked reduction in PICC-related complications (bacteraemia, thrombosis, obstruction and accidental withdrawal) following the provision of a training programme for nurses in the use of ultrasound techniques for venous cannulation. Implementation of this programme also reduced variability among other health professionals involved (radiologists, surgeons and anaesthetists), producing cost savings of 270-305 Canadian dollars for each catheter inserted. A similar programme, conducted in Texas, USA, achieved a 74% reduction in the number of CVCs inserted (including intensive care), mainly by replacing them with PICCs, which were inserted by nurses trained in the use of ultrasound techniques (15). This intervention reduced costs by $200,000 per year, or $1,614 per PICC inserted.

Risk factors for difficult peripheral intravenous cannulation

It has been argued that strategies should be promoted to avoid multiple puncture and the undesirable effects of central access catheterisation (16). Although there is a growing body of evidence in favour of cannulation support methods (ultrasound, infrared and transillumination), few studies have attempted to identify risk factors for DPIVC or the profiles of patients likely to present it. To our knowledge, the only studies conducted in this area, to date, have been limited to specific hospital areas (intensive care, Accident and Emergency (A&E), paediatrics and oncology), and so there is little scope for comparing different approaches. Specifically, it has been suggested that several advanced chronic conditions may contribute to the progressive degradation of the peripheral vascular tree, such as obesity, vasculopathy and chronic pluripathology (7,17–20). However, these studies focus on the application of ultrasound to improve the effectiveness of puncture techniques, and so their approach to potential risk factors should be considered with caution.

In the context of hospital A&E services, three earlier studies have made interesting findings.

Sebbane et al. conducted a study in France in 2013, without a control group, evaluating risk factors that determine the success of the first attempt at cannulation (21). These authors observed an association between extreme values for body mass index and the appearance of DPIVC, which was also associated with poor assessment by the health professional (whether doctor or nurse) of the viability of access. In fact, the professional's view of the feasibility of cannulation has been explored in various studies, many of which have found it to be a relevant factor and a possible predictor of difficulty in obtaining venous access (22). Another study concluded that certain variables related to the professional who performs the technique, regarding his/her professional experience in general and concerning venous cannulation in particular, may also influence the effectiveness of the intervention (23).

In 2016, Carr et al. performed a cohort study which sought to identify factors relevant to the success of venous cannulation in patients treated at hospital A&E units (24). These authors, too, highlighted the importance of the professional's assessment of the viability of venous access (visibility and palpability of the vein), in addition to factors such as cachexia (wasting syndrome) and advanced age, which were potentially associated with difficulty. This study also identified differences related to the location of the vein to be punctured and to the cannulation experience of the clinician performing the technique.

Finally, Fields et al. reported that previous pathological conditions, such as diabetes, parenteral drug abuse and spindle cell disease, can increase the risk of DPIVC (25). Other relevant factors, although to a lesser extent, were previous episodes of puncture difficulty and the need for puncture support systems, observed in previous contacts with the patient.

In view of this background, we consider it necessary to analyse, in a single study, the different variables that have been proposed as potential risk factors for difficulty in cannulation, including care settings other than hospital A&E units.

In this project, we aim to identify the risk factors affecting patients with DPIVC, and to determine the weight of each of these factors, so that a model can be established by means of which patients at risk can be identified at an early stage and so that puncture

support methods can be prioritised (26), taking into account that the use of such methods is increasingly recommended (27).

METHODOLOGY

Hypothesis

The presence of potential risk factors considered in the study will independently increase the risk of the patient to present difficulty during peripheral venous cannulation.

Aims

The main study goal is to identify the possible risk factors associated with the patient, thus enabling us to establish a model with which to estimate the probability of difficult access to venous cannulation in hospital treatment.

Secondary goals:

- To determine the characteristics of patients with DPIVC according to different care profiles (medical hospitalisation, surgical hospitalisation, surgical area and A&E-intensive care).
- To describe the type of venous catheter insertion technique according to the appearance of difficulty in cannulation: number of punctures required, perception of pain, resources needed (number of professionals and estimated time required) and need for alternative methods (CVC, ultrasound support, referral to other professionals).
- To determine whether the occurrence of such difficulty is influenced by the experience and characteristics of the health professional involved.

Methods and analysis

Design. Case-control study with incident cases.

Settings. 48 units, corresponding to different care settings: A&E, intensive care, surgical area and hospitalisation units, in eight public hospitals in the Spanish National Health System, with diverse profiles, including three university hospitals and five second-level hospitals.

Subjects. Adults (18 years old or more) for whom peripheral pathway cannulation is performed or attempted, and who consent to participate in the study. Patients in emergency situations and women during childbirth or puerperium will be excluded.

Data collection. The nurse who performs the technique will record, in an anonymised record, the variables related to the intervention and the patient's medical history number. All nurses may add such records during the study period, from February 1st to December 31st 2017. Members of the research team will retrospectively review the medical history to compile the health variables. The data collection system was piloted in four of the above hospital units in February 2016.

All patients in the sample population who present DPIVC at some time will be included in the case group if they meet at least one of the following conditions: two or more failed punctures; the need for puncture support techniques (ultrasound, infrared or transillumination) when accessible vessels cannot be identified (excluding ultrasound scans for other purposes); the need for central access after failure to achieve peripheral access or decision not to implement it (no venous access achieved and the procedure is abandoned). Subsequently, we will determine the distribution of the incidence of DPIVC by hospital environments (medical hospitalisation units, surgical hospitalisation units, surgical area and A&E-intensive care). To offset the effects of possible differences in the inclusion of patients and their different profiles according to the units participating in the study, the control group will be selected by random sampling stratified by the same treatment environments, following the distribution of incidence observed in the case group. This sample will be composed of the patients included in the study who do not present the conditions for selection to the case group. Three controls will be selected for each case. The nurses will be blinded to the selection criteria for cases and controls, in order to avoid selection bias.

Since the study will require the involvement of a significant number of professionals from different environments, a team of collaborators has been recruited, all of them Registered Nurses, to coordinate the study in their respective units and centres, thus serving as a bridge between the research team and the other professionals.

Variables and definitions. Taking into account previous studies in this field, 13 variables will be hypothesised as possible risk factors. Variables will also be considered to assess the comparability of the case and control groups. Table 1 lists these variables and their definitions.

TABLE 1. Variables and definitions

VARIABLE	DEFINITION
Variables analysed to assess the comparability of groups:	
Age (continuous quantitative)	
Sex (qualitative)	
Specialist area (qualitative)	Hospital area where treatment is provided.
Reason for admission (qualitative)	Main diagnosis on admission; pathologies grouped by diagnostic group according to the International Classification of Diseases.
Variables regarding the cannulation technique:	
Arterial blood pressure before cannulation (continuous quantitative)	
Number of punctures made (continuous quantitative)	
Catheter inserted (yes/no) (qualitative)	
Calibre of catheter inserted	
RN (continuous quantitative)	Number of nurses participating.
NA (continuous quantitative)	Number of nursing assistants participating.
Time (continuous quantitative)	Estimated time, in minutes, spent implementing the technique, by all professionals.
Pain intensity after implementation of the technique (continuous quantitative)	Evaluation of pain perceived by the patient after cannulation, measured on a Visual Analogue Scale.
Need for alternative methods or techniques (qualitative): • Central venous catheter • Ultrasound, infrared or transillumination • Referral to other professionals or hospital services • Access via lower limbs or other alternative locations.	

Rejection of cannulation, in favour of (qualitative): • Oral route. • Subcutaneous route. • Nasogastric tube. • Central venous catheter. • Other.	
Variables hypothesised as risk factors for DPIVC:	
Age (qualitative, 4 categories)	
Non-palpable vein (qualitative)	Vein not palpable, in the opinion of the nurse performing the technique.
Non-visible vein (qualitative)	Vein not visible, in the opinion of the nurse performing the technique.
History of DPIVC (qualitative)	Known history of DPIVC. Evidence in the patient's medical history of difficulty in obtaining a venous route, or the patient describes such a difficulty in a previous experience.
Upper-limb alterations (qualitative)	Visible alterations in the upper extremities: oedema, haematoma, inflammation, surgical interventions, medical devices or any other circumstance that hinders or limits the puncture. If any such alteration is present, we will distinguish between acute alterations (less than three months from appearance) and chronic or permanent alterations (qualitative variable with three categories).
Previous punctures (qualitative)	Punctures carried out before the present episode. During the present treatment episode, a venous catheter has previously been inserted (or insertion has been attempted).
Previous episodes (qualitative)	Hospitalisation or A&E attention during the last 90 days.
Diabetes mellitus (qualitative)	
Parenteral drug abuse (qualitative)	Documented history or current use of parenteral drugs.

Chemotherapy (qualitative)	Chemotherapy now or during the last 90 days.
BMI (qualitative)	Body mass index. Only extreme values have been associated with DVIPC, and so this parameter will be compiled as a qualitative variable, with three categories: <18.5; 18.5-30; >30.
HD(qualitative)	Haemodialysis programme. Documented history or current use of a long-term programme of haemodialysis.
COPD (qualitative)	Chronic obstructive pulmonary disease.
Variables related to the nurse performing the cannulation technique:	
Experience (years) (continuous quantitative)	Years of nursing experience.
Technique (years) (continuous quantitative)	Years of experience in peripheral venous cannulation. Number of years during which the nurse has worked in settings where peripheral venous cannulation is regularly performed.
Age (continuous quantitative)	
Sex (qualitative)	

Sample. The minimum sample size was calculated taking as a reference the risk factor "diabetes" from the study of A&E patients conducted by Fields et al. in 2014 (5). Assuming an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral test, we calculated that 87 cases and 261 controls would be required to detect a minimum odds ratio of 2.1, assuming a rate of exposure of 0.5 in the control group. In this consideration, the Poisson method was used. In addition, another ten cases were attributed by category, following the system described by Peduzzi et al. (28), and so the total minimum sample required is 207 cases. Assuming a frequency of 10%, 2070 patients must be identified to achieve the population size required for the case group. The estimated time to reach this sample size is ten months, although this could be extended if necessary.

Data analysis. A descriptive analysis of the variables will be performed, including the distribution of the phenomenon by hospital environments and services (type of attention). Tests of association will be applied between the main study variables:

hypothetical risk factors, characteristics of the technique, environment, and experience of the professional. The association will be determined by bivariate analysis based on chi-square, Student's t, Mann-Whitney U, Wilcoxon W and Friedman tests, ANOVA and Pearson and Spearman correlations, depending on the nature and normality of distribution of the variables. Subsequently, the variables hypothesised as risk factors for the onset of DPIVC will be analysed using a logistic regression model, to obtain the respective adjusted odds ratios.

Validity and reliability / Rigour

The fact that cases and controls will be recruited from the same source, together with the inclusion of sample adjustment variables, will ensure the reliable comparability of the groups.

The control group will be distributed by stratified random sampling, which will ensure the homogeneity of the case and control groups.

Blinding to the study hypothesis and to the variables hypothesised as risk factors will prevent any selection bias that might arise in the nurses participating in the data collection process.

Relevant variables will be considered in order to study the possible influence of the professional profile of the nurse performing the technique on the appearance of DPIVC.

The multicentre nature of the study and the inclusion of different hospital profiles, and of hospitals located in different geographic areas, will enhance the diversity of the sample and its external validity.

Limitations

The variable "spindle cell disease" is not included in our study because of its low prevalence in the reference population. Since our study focuses on patient risk factors, variables related to the nurse's experience have not been hypothesised as potential risk factors. An association analysis of these variables will be conducted to determine whether future studies in this regard are needed.

Ethics and dissemination

The study does not involve intervention or change in usual practice. The patients will be asked by the clinician nurse to give their signed informed consent, and will be provided with clearly-written information about the purpose and implications of the research.

The computerised database does not contain patient identification. The individuals involved in compiling data will sign a confidentiality agreement.

The project has been peer evaluated and approved by the reference Research Ethics Committee (code IB3137/16PI) and by the research committees of each of the participating centres.

The results of this study will be sent to a peer-reviewed scientific journal for publication.

DISCUSSION

The proposed study will enable us to obtain profiles of patients at risk of difficulty in peripheral venous cannulation. Identifying this risk at an early stage will facilitate the early and selective use of puncture support methods such as ultrasound or infrared imaging.

Nurse-led intravenous treatment teams can use this information to identify priority patients and to ensure the appropriateness of the interventions made. The information obtained regarding the use of nursing resources for managing DPIVC may also be useful for these teams.

AUTHOR CONTRIBUTIONS

All authors have agreed on the final version and meet both of the following criteria [recommended by the ICMJE (http://www.icmje.org/ethical_1author.html)]:

- substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content.

MARC coordinates the research team and is responsible for reporting Ethic Committees and every institution involved in the study . MARC and IBM revised previous literature about puncture difficulty in adults, and designed data collection methods along with LJMB, IFF, CMM and LMM. JEPG and JMMA audited the study design, especially concerning statistical analysis proposed. IFF designed and maintains the database to ensure data validity. MARC, IBM, JEPG and JMMA wrote first version of the protocol, which was later edited by all the authors.

FUNDING STATEMENT

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COPETING INTERESTS STATEMENT

The authors have no conflict of interest to declare.

DATA SHARING STATEMENT

Anonymised data from this study will be incorporated in an automatized data file registered by the Spanish Agency of Data Protection. We shall make data obtained from this study available to the scientific community via scientific publications. Further information regarding research strategy and future publications are available in request to the corresponding author.

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Risk factors for difficult peripheral venous cannulation in hospitalised patients. A multicentre case-control study protocol

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	*(a) Indicate the study's design with a commonly used term in the title or the abstract* Both title (page 1) and abstract (page 2) contain explicit information about case-control design
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found The abstract includes information about methods and data collection, statistical analyses intended to be done, as well as potential utility of results.
Introduction		
Background/rationale	2	*Explain the scientific background and rationale for the investigation being reported* Pages 4 and 5 offer information about previous studies addressing venous access in general, and difficult peripheral venous access in particular. In pages 5 and 6, we present previous studies about potential risk factors and gaps to be covered with our research.
Objectives	3	*State specific objectives, including any prespecified hypotheses* Page 7: conceptual hypothesis and aims.
Methods		
Study design	4	*Present key elements of study design early in the paper* Page 7
Setting	5	*Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection* Pages 7-8. Description of settings (48 units of 8 public hospitals) and the processes of data collection.
Participants	6	*(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls* In page 8 we describe subjects and inclusion/exclusion criteria.
		(b) For matched studies, give matching criteria and the number of controls per case
Variables	7	*Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable* Page 8: 'Variables and definitions'. Table 1 offers further information about every variable included in the study.
Data sources/ measurement	8*	*For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment*

		methods if there is more than one group Page 8 (variables) and Table 1.
Bias	9	*Describe any efforts to address potential sources of bias* In page 9 ('Validity and reliability / rigour') we describe efforts to reduce risk of bias, especially regarding data collection and comparability of groups.
Study size	10	*Explain how the study size was arrived at* Sample size and number of controls per case are described in page 9, 'sample'.
Quantitative variables	11	*Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why*
Statistical methods	12	*(a) Describe all statistical methods, including those used to control for confounding* Statistical methods are described in page 9, 'Data analysis'. Some variables regarding professional expertise of the nurse are used as potentially confounding factors.
		(b) Describe any methods used to examine subgroups and interactions Page 9, 'Data analysis'. This study will explore the distribution of venous cannulation difficulty in different environments (settings), which has never been explored in a single study.
		(c) Explain how missing data were addressed
		(d) If applicable, explain how matching of cases and controls was addressed
		(e) Describe any sensitivity analyses
Results *(not applicable in protocol reporting)*		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	*Summarise key results with reference to study objectives*
Limitations	19	*Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias* Limitations are described in page 10
Interpretation	20	*Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence* As there are not available results to be discussed, we include in 'Conclusions' (page 10) some aspects regarding the utility of our investigation and data applicability.
Generalisability	21	*Discuss the generalisability (external validity) of the study results*
Other information		
Funding	22	*Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based* Page 11, funding statement