

1. Title and structured project summary

Scientific title

Protocol: “Efficacy and safety of central venous catheter placement in the internal jugular vein using an ultrasound-guided technique versus the anatomical landmark technique in critically ill paediatric patients: a randomised clinical trial”.

Public title

Ultrasound-guided central venous catheter placement versus the anatomical landmark technique in critically ill children.

Summary

Introduction

Critically ill paediatric patients often require central venous catheter (CVC) placement for administration of fluids, vasoactive drugs, blood products and parenteral nutrition, as well as for blood sampling and haemodynamic monitoring. The anatomical landmark technique (ALT) has been widely used for CVC placement in the internal jugular vein; however, it may be associated with cannulation failure and mechanical complications. The ultrasound-guided technique (TGUS) has shown benefits in adults, but evidence in critically ill paediatric patients, particularly in the Paediatric Intensive Care Unit (PICU), remains limited. Therefore, it was considered necessary to compare both techniques in critically ill paediatric patients.

Objective

To compare the efficacy and safety of central venous catheter placement in the internal jugular vein using an ultrasound-guided technique versus the anatomical landmark technique in critically ill paediatric patients.

Study design

This was a randomised, controlled, parallel-group, single-centre, single-blind clinical trial with a 1:1 allocation ratio and a superiority framework. Retrospective registration was requested from ISRCTN. Registration number pending.

Study setting

Paediatric Intensive Care Unit of High Specialty Medical Unit No. 48, Gynecology-Pediatrics Hospital, Mexican Social Security Institute, León, Guanajuato, Mexico.

Participants

Critically ill paediatric patients aged from 1 month to 15 years and 11 months, of either sex, admitted to the Paediatric Intensive Care Unit and requiring CVC placement in the internal jugular vein as part of their clinical management were included, provided that informed consent had been obtained from the father, mother or legal guardian before the procedure and assent had been obtained from the minor when applicable.

Exclusion criteria were haematological malignancies associated with active coagulation disorders, ongoing anticoagulant therapy, malformation at the puncture site, and refusal by the father, mother or legal guardian to provide informed consent. Withdrawal/elimination criteria were voluntary withdrawal from the protocol by the father, mother or legal guardian; voluntary discharge before completion of protocol-defined follow-up; transfer to another hospital unit preventing follow-up and outcome assessment; incomplete medical records preventing verification of essential analytical data; absence of essential procedure or primary outcome data that could not

be recovered from the data collection form, clinical record, medical notes, nursing records or imaging studies; and major protocol deviation preventing assessment of the assigned technique or compromising the validity of the primary outcome.

Interventions

Participants were assigned to one of two interventions. The intervention group underwent CVC placement in the internal jugular vein using real-time ultrasound guidance and the Seldinger technique. The control group underwent CVC placement in the internal jugular vein using the anatomical landmark technique and the Seldinger technique. In both groups, catheter position was confirmed by imaging according to availability and clinical judgement.

Randomisation

Allocation was performed in a 1:1 ratio by simple randomisation using a coin toss at the time of the procedure. “Heads” assigned the participant to the ultrasound-guided technique and “tails” assigned the participant to the anatomical landmark technique. Each participant was randomised only once and only the first included procedure per patient was analysed.

Blinding

Because of the nature of the procedure, the operator could not be blinded. However, procedural data were recorded using a standardised data collection form and were subsequently coded in an electronic database. Efficacy and safety assessment and the statistical analysis were performed with coded groups, maintaining blinding of the principal investigator during the analysis.

Primary outcome

The primary outcome was efficacy of CVC placement, defined as successful cannulation of the internal jugular vein, confirmed by imaging, with a maximum of two attempts and within no more than 20 minutes from the first venous puncture to catheter placement.

Secondary outcomes

The key secondary outcome was safety of CVC placement for each intervention. Safety was assessed by the absence of serious immediate complications and by the presence of two or fewer non-serious complications, such as inadvertent puncture of the internal carotid artery not causing arterial thrombosis, air embolism or vascular injury, and venous or arterial haematoma at the puncture site not causing internal jugular vein thrombosis, vascular injury, displacement or airway collapse.

Secondary outcomes included number of attempts, CVC placement time, failed cannulation, immediate, intermediate and late complications, type and number of complications, and catheter-related infection.

Sample size

The planned sample size was 98 patients, 49 per group, calculated to compare two independent proportions of successful cannulation, with a two-sided alpha of 0.05 and 80% statistical power. During the study, 73 patients were recruited. The trial was stopped early after an internal institutional analysis because of evidence of greater efficacy of the ultrasound-guided technique.

Statistical analysis

Qualitative variables were described using frequencies and percentages. Quantitative variables were described using mean and standard deviation or median and interquartile range, according to their distribution. Normality

was assessed using the Kolmogorov-Smirnov test. Between-group comparisons used the chi-squared test or Fisher exact test for categorical variables, and Student t test or Mann-Whitney U test for numerical variables. Measures of association and clinical impact were estimated, including relative risk and number needed to treat, with 95% confidence intervals. Statistical significance was set at $p < 0.05$.

Ethics review

The protocol was approved by the Local Health Research Ethics Committee on 12 June 2019 and by the Local Health Research Committee on 20 June 2019, with institutional registration number R-2019-1002-028. Informed consent was obtained from the father, mother or legal guardian, and assent was obtained from the minor when applicable.

Source of monetary or material support

The study had no external funding. Human resources, materials, ultrasound equipment, catheters and infrastructure were provided by High Specialty Medical Unit No. 48, Gynecology-Pediatrics Hospital, IMSS, as part of usual care for critically ill paediatric patients.

Primary sponsor

High Specialty Medical Unit No. 48, Gynecology-Pediatrics Hospital, Mexican Social Security Institute.

Country of recruitment

Mexico.

Health condition or problem studied

Central venous catheter placement in the internal jugular vein in critically ill paediatric patients.

Contact for public and scientific queries

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2. General administrative information

Full title: "Efficacy and safety of central venous catheter placement in the internal jugular vein using an ultrasound-guided technique versus the anatomical landmark technique in critically ill paediatric patients. Randomised clinical trial".

Institutional protocol number: R-2019-1002-028.

Protocol version: Version 5.0, 2026, for retrospective registration in ISRCTN. Date of approval by the Local Health Research Ethics Committee: 12/06/2019. Date of approval by the Local Health Research Committee: 20/06/2019.

Public trial registration: registration number pending.

Sponsor/funding source: no external sponsor; institutional resources from UMAE No. 48, IMSS. The institution did not influence the analysis or publication.

Responsible investigator: Dr Gloria Patricia Sosa Bustamante. Collaborating investigator 1: Dr Alma Patricia González. Collaborating investigator 2: Dr Carlos Paque Bautista. Collaborating investigator 3: Dr Beatriz

González Yebra. Collaborating investigator 4: Arturo Maximiliano Reyes-Sosa. Collaborating investigator 5: María Regina Soto-Domínguez. Collaborating investigator in the PICU: Dr Israel Sinahi Moreno Aguirre. Two operators: expert paediatric intensivists. Assistant 1: attending physician on duty. Assistant 2: specialist nurse on duty.

3. Roles and responsibilities

3A. Investigator contributions

Israel Sinahi Moreno-Aguirre (ISMA), Beatriz González-Yebra (BGY), María Regina Soto-Domínguez (MRSD), Alma Patricia González (APG), Carlos Paque-Bautista (CPB), Arturo Maximiliano Reyes-Sosa (AMRS), Gloria Patricia Sosa-Bustamante (GPSB).

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2. University of Guanajuato, León Campus, Division of Health Sciences, Department of Medicine and Nutrition, León, Guanajuato, Mexico.

3. Mexican Social Security Institute, Bajío National Medical Centre, High Specialty Medical Unit, Gynecology-Pediatrics Hospital No. 48, Directorate of Health Education and Research, León, Guanajuato, Mexico.

Conceptualisation: ISMA, MRSD, GPSB.

Methodology: GPSB, BGY, ISMA, APG, CPB.

Investigation: APG, CPB, ISMA.

Data curation: ISMA, BGY, MRSD, APG.

Formal analysis: ISMA, MRSD, APG, GPSB, BGY.

Validation: BGY, APG, CPB.

Project administration: ISMA, BGY, APG, CPB.

Supervision: APG, CPB, BGY.

Resources: ISMA, APG, CPB.

Funding acquisition: not applicable. The project was funded by the hospital where the research protocol was conducted.

3B. Sponsor

The study had no external sponsorship. All resources used belonged to Gynecology-Pediatrics Hospital No. 48 of the Mexican Social Security Institute, a public governmental organisation. Address: IMSS UMAE 48, Paseo de los Insurgentes S/N, Los Paraísos, 37328, León, Guanajuato, Mexico. Telephone: +52 477 174 800.

3C. Role of institution

The institution provided infrastructure and healthcare resources but did not participate in the statistical analysis, interpretation of results or decision to publish.

3D. Committees and oversight

The research committee supervised protocol conduct and the reporting of deviations during implementation. There was no external assessment committee because this was a single-centre study. The research team could

propose suspension; institutional review and recommendation corresponded to the Local Research Committee and/or Ethics Committee.

4. Open science: trial registration

The institutional registration number was R-2019-1002-028. Approval letters from the ethics and research committees are attached. Registration is being performed retrospectively in the ISRCTN Registry; the registration number is pending. The clinical trial has been completed. The URL and registration number will be added once registration is obtained.

5. Protocol and statistical analysis plan

The protocol will be accessible in the institutional repository of the University of Guanajuato or by request to the responsible investigator via email at gloria.sosa@imss.gob.mx. The statistical analysis plan is described in the research protocol and will be reported in the publication. The statistical analysis plan is incorporated into the protocol.

6. Open science: data sharing

Individual de-identified data may be requested from the responsible investigator by email at gloria.sosa@imss.gob.mx. In addition to the data, the variable dictionary and statistical design will be available after the main publication upon reasonable request, institutional approval and a data use agreement.

7. Funding and conflicts of interest

The study had no external or private funding. There was no support from manufacturers of ultrasound devices, catheters or supplies, and no commercial funding. The authors declare that they have no conflicts of interest.

8. Dissemination policy

The study results will be disseminated through presentation at scientific congresses and publication in an indexed biomedical journal. Once available, resulting publications will be incorporated into the ISRCTN record to promote transparency and accessibility of results. Authorship of publications derived from the study will be determined according to the criteria of the International Committee of Medical Journal Editors (ICMJE). All authors must have made substantial contributions to study design, conduct, analysis or interpretation of data, participated in drafting or critically revising the manuscript, and approved the final version before publication.

9. Introduction, background and rationale

Central venous catheter (CVC) placement is an essential procedure in critically ill paediatric patients because it enables haemodynamic monitoring, administration of fluids, drugs, blood products and parenteral nutrition, and blood sampling. In children, especially infants and preschool children, central venous cannulation may be more complex than in adults because of smaller vascular diameter, anatomical variation, lack of patient cooperation and clinical conditions inherent to critical illness [1-3].

For many years, the anatomical landmark technique (ALT) was the conventional method for CVC placement. With the development of ultrasound (US), ultrasound-guided technique has become a widely recommended strategy in adults, associated with higher success rates, fewer attempts and fewer mechanical complications [4-6]. However, this evidence cannot be directly extrapolated to paediatric patients because of anatomical, physiological and clinical differences, and because of the limited availability of randomised clinical trials in critically ill children [7-9].

Complications associated with CVC placement include arterial puncture, haematoma, pneumothorax, haemothorax, vascular injury, air embolism, arrhythmias, catheter-related infection and device dysfunction. The

frequency of complications reported in the literature ranges approximately from 5% to 29%, depending on centre experience, operator, number of attempts, coagulation status, age, weight, puncture-site anatomy and clinical condition [10-12]. These complications may increase morbidity, prolong hospital stay, increase costs and require additional interventions [10,11].

Ultrasound allows identification of the vein, artery and anatomical variants before and during the procedure. It may be used as a static/previsualisation technique or as a dynamic real-time technique, with short-axis or long-axis approaches. Although its use offers technical advantages, it requires specific training, operator experience and suitable equipment, which may limit implementation, particularly in small children and in centres with fewer resources [4,13,14].

Available paediatric evidence is heterogeneous. Some clinical trials and meta-analyses have shown that ultrasound guidance may increase success rates and reduce the number of attempts and arterial punctures [8,15,16], whereas other studies have not demonstrated significant differences in complications or placement time [7,17]. Moreover, much of the paediatric evidence comes from elective procedures performed in the operating theatre in haemodynamically stable patients, which differs from the Paediatric Intensive Care Unit (PICU) setting, where patients often have haemodynamic instability, difficult vascular access and severe clinical conditions [8,9,18].

In critically ill paediatric patients, the clinical context may substantially affect the performance of both techniques. Age, weight, haemodynamic status, anatomical variability, urgency of the procedure and operator experience may influence success rate, number of attempts, placement time and occurrence of complications [13,18,19]. Therefore, well-designed studies comparing both techniques at the same anatomical site, particularly the internal jugular vein, in a non-elective setting such as the PICU are needed [8,9,16].

In this context, the present clinical trial evaluated the efficacy and safety of CVC placement in the internal jugular vein using ultrasound guidance compared with the anatomical landmark technique in critically ill paediatric patients. This comparison was relevant to determine whether ultrasound could improve procedural efficacy, reduce failed attempts, shorten placement time and promote safer and more timely care in the PICU [8,16,18].

Rationale

Central venous catheter placement is a frequent and essential procedure in critically ill paediatric patients because it enables administration of fluids, vasoactive drugs, parenteral nutrition and haemodynamic monitoring. However, placement may be associated with serious mechanical complications, increased hospital stay, greater morbidity and a potential increase in mortality.

Although the ultrasound-guided technique has demonstrated benefits in adults, the available evidence in critically ill paediatric patients remains limited, particularly in intensive care settings and in countries with variable technological resources and training. In many centres, including many hospitals in developing countries, the anatomical landmark technique continues to be widely used.

High Specialty Medical Unit No. 48 cares for a considerable number of critically ill paediatric patients each year who require central venous access. Therefore, it was necessary to compare the efficacy and safety of ultrasound guidance with the anatomical landmark technique to identify which approach provides better clinical results. This study sought to provide evidence that may contribute to improving quality and safety of care, reducing procedure-related complications and strengthening future clinical recommendations for CVC placement in critically ill paediatric patients.

10. Objectives and hypotheses

General objective

To compare the efficacy and safety of central venous catheter placement in the internal jugular vein using the ultrasound-guided technique versus the anatomical landmark technique in critically ill paediatric patients.

Specific objectives

To establish the efficacy of central venous catheter placement with both techniques in critically ill paediatric patients.

To determine the safety of central venous catheter placement with both techniques in critically ill paediatric patients.

To compare whether differences existed between the efficacy and safety of central venous catheter placement using the ultrasound-guided technique versus the anatomical landmark technique in critically ill paediatric patients.

Hypotheses

Null hypothesis

There was no difference in the efficacy and safety of central venous catheter placement in the internal jugular vein using the ultrasound-guided technique versus the anatomical landmark technique in critically ill paediatric patients.

Alternative hypothesis

There was a difference in the efficacy and safety of central venous catheter placement in the internal jugular vein using the ultrasound-guided technique versus the anatomical landmark technique in critically ill paediatric patients.

11. Methods: patient and public involvement

There was no formal involvement of patients, carers or public representatives in the methodological design because of the nature of the study and the urgent procedural intervention performed in the PICU. The protocol was developed by the research team based on the clinical need identified in the Paediatric Intensive Care Unit and on available evidence regarding CVC placement in critically ill paediatric patients. However, parents or legal guardians of eligible patients participated in the informed consent process, and paediatric patients aged 8 to 15 years and 11 months participated through written assent when they were awake, conscious, not sedated and clinically able to understand the information provided. Information provided to parents, guardians and minors was explained in clear language and included the purpose of the study, the nature of each technique, potential risks, expected benefits, voluntariness of participation and the right to withdraw from the study without affecting the medical care received.

12. Methods: trial design

This was a randomised, controlled, parallel-group, single-centre, single-blind clinical trial with a 1:1 allocation ratio. The trial compared two techniques for CVC placement in the internal jugular vein in critically ill paediatric patients: ultrasound-guided technique versus anatomical landmark technique.

The conceptual framework was superiority, because the study sought to determine whether the ultrasound-guided technique achieved greater overall efficacy than the anatomical landmark technique. The unit of randomisation was the patient requiring CVC placement during admission to the Paediatric Intensive Care Unit.

Participants were randomly assigned to one of two interventions: intervention group, ultrasound-guided CVC placement; or control group, CVC placement using the anatomical landmark technique. Allocation was

performed at the time of the procedure by coin toss, with an expected 1:1 allocation ratio. Each participant was randomised only once and only the first procedure per patient was analysed.

The study had a pragmatic, procedural design because both techniques are part of usual clinical practice for obtaining central venous access in critically ill paediatric patients. Interventions were performed under real-care conditions in the Paediatric Intensive Care Unit by paediatric intensivists trained and standardised in both techniques.

Because the interventions were visible, neither the operator nor the clinical staff present during the procedure could be blinded. However, the trial was considered single-blind because outcome assessment and statistical analysis were performed with coded groups.

13. Trial setting

The study was conducted in a tertiary hospital, in the Paediatric Intensive Care Unit of High Specialty Medical Unit No. 48, Gynecology-Pediatrics Hospital, Mexican Social Security Institute, located in León, Guanajuato, Mexico.

Recruitment was conducted among paediatric patients admitted to the Paediatric Intensive Care Unit who, at admission or during their hospital stay, required a central venous catheter in the internal jugular vein as part of their treatment. Patients aged from 1 month to 15 years and 11 months, of either sex, who met the selection criteria and whose parents or legal guardians provided informed consent were included; assent from the minor was also obtained when applicable.

The study was single-centre. The unit had the necessary human, physical and material resources to perform both interventions, including trained paediatric intensivists, inpatient and PICU areas, clinical records, Philips 7500 ultrasound equipment, central venous catheters and material available for CVC placement 24 hours per day.

Procedures were performed by paediatric intensivists experienced in CVC placement and trained in the use of ultrasound for vascular access. The unit also had resources for immediate management of complications, including resuscitation equipment, ventilators, vasoactive drugs, material for pleural drainage and availability of a paediatric surgeon 24 hours per day.

14. Eligibility criteria

14a. Participant eligibility criteria

Eligible participants were critically ill paediatric patients admitted to the Paediatric Intensive Care Unit of UMAE No. 48, Gynecology-Pediatrics Hospital, Mexican Social Security Institute, who required CVC placement in the internal jugular vein during admission or hospital stay.

Inclusion criteria

- Patients of either sex.
- Age from 1 month to 15 years and 11 months at the time of the procedure.
- Hospitalisation in the Paediatric Intensive Care Unit of UMAE No. 48, Gynecology-Pediatrics Hospital.
- Clinical requirement for CVC placement in the internal jugular vein.
- Informed consent provided by the father, mother or legal guardian before the procedure.
- Assent from the minor when applicable, in patients aged 8 to 15 years and 11 months who were awake, conscious, not sedated and clinically able to understand the information provided.

Exclusion criteria

- Haematological malignancies associated with active coagulation disorders, defined by any of the following: prothrombin time greater than 18 seconds, activated partial thromboplastin time greater than 55 seconds or platelet count lower than $50 \times 10^9/L$.
- Ongoing anticoagulant therapy at the time of the procedure.
- Anatomical malformation, local lesion, infection at the puncture site or structural condition preventing safe catheter placement in the internal jugular vein.
- Refusal by the father, mother or legal guardian to provide informed consent.

Elimination or withdrawal criteria after randomisation

- Voluntary withdrawal from the protocol by decision of the father, mother or legal guardian.
- Voluntary patient discharge before completing the protocol-defined follow-up.
- Transfer to another hospital unit preventing follow-up and outcome assessment.
- Incomplete clinical record preventing verification of essential analytical data.
- Absence of essential procedure or primary outcome data that could not be recovered through review of the data collection form, clinical record, medical notes, nursing records or imaging studies.
- Major protocol deviation preventing assessment of the assigned technique or compromising validity of the primary outcome.

Participants eliminated or withdrawn after randomisation were documented with the specific cause for elimination or withdrawal. When verifiable procedural and primary outcome data were available, participants were considered for the main analysis according to the statistical strategy defined in the protocol.

14b. Eligibility criteria for the centre and operators

Eligible operators were paediatric intensivists assigned to the Paediatric Intensive Care Unit, with experience in CVC placement using the Seldinger technique and formal training in ultrasound for vascular access. Before trial initiation, operators were standardised in both placement techniques. Procedures were performed by two main operators, both with more than 8 years of experience in paediatric intensive care and training in ultrasound-guided CVC placement.

Before the trial began, operator performance was assessed. CVC procedures performed during the previous year using the anatomical landmark technique were reviewed for each operator. Subsequently, 15 procedures using the ultrasound-guided technique were evaluated for each operator. The frequency of successful cannulation and procedure-related complications was compared between operators. Dichotomous variables were analysed using the chi-squared test or Fisher exact test, as appropriate, and absolute differences in proportions with 95% confidence intervals were estimated. No relevant differences between operators in efficacy or safety were identified; therefore, they were considered to have very similar performance for both techniques during the study.

15. Intervention and comparator

15a. Description of the intervention and comparator

The trial compared two techniques for CVC placement in the internal jugular vein in critically ill paediatric patients: ultrasound-guided technique and anatomical landmark technique.

Intervention A: ultrasound-guided CVC placement

The intervention consisted of CVC placement in the right or left internal jugular vein using the Seldinger technique under real-time ultrasound guidance. A Philips 7500 ultrasound machine available in the hospital unit was used, with a linear transducer in vascular mode to visualise the internal jugular vein. In small patients, when

the operator considered it necessary, a sector transducer in vascular mode was used. Before the procedure, ultrasound was used to assess the vascular anatomy of the internal jugular vein bilaterally, and the operator selected the anatomical puncture site according to the patient's clinical and anatomical conditions.

After preparation of materials and the sterile field, the ultrasound equipment was covered in sterile fashion. The internal jugular vein was identified by ultrasound in short-axis mode (out of plane), puncture was guided in real time, needle position within the vein was confirmed, followed by confirmation of the guidewire position and finally the catheter position within the vessel. CVC location was confirmed by chest radiography or echocardiography according to availability and clinical judgement.

Intervention B: anatomical landmark technique

The control intervention consisted of CVC placement in the right or left internal jugular vein using the Seldinger technique based on anatomical landmarks. The operator chose the left or right anatomical site at the time of the procedure. Under sterile conditions, the patient's head was turned contralaterally to the puncture site, with cervical hyperextension and a 20° Trendelenburg position. Anatomical landmarks were identified, including the sternocleidomastoid muscle, sternal notch and clavicle. The internal jugular vein was then punctured, venous return confirmed, the guidewire introduced, the needle removed, the dilator passed and finally the CVC placed. Catheter position was confirmed by chest radiography or ultrasound as appropriately positioned.

In both groups, antisepsis was performed with 2-4% chlorhexidine, sterile barrier precautions were used, local infiltration with 1% lidocaine was administered, the catheter was flushed with heparinised 0.9% saline, patency and venous return in all lumens were verified, and the CVC was secured to the skin with 3-0 nylon suture. Catheter calibre and length were selected according to the patient's age and characteristics. The unit had Arrow® and Bioflux® central venous catheters of different calibres and lengths, as well as material available for CVC placement 24 hours per day.

When procedures were unsuccessful, they were considered failures, and the CVC was placed at another anatomical site using ultrasound guidance, puncture or venous cut-down to ensure care of the critically ill patient.

15b. Criteria for discontinuing or modifying the assigned intervention

The assigned intervention could be discontinued or modified when, during the procedure, the operator identified a condition that increased risk to the patient or prevented safe continuation of the assigned technique. These conditions included severe haemodynamic instability, failure of the cannulation technique, immediate complication during the procedure, acute clinical deterioration, or the judgement of the responsible paediatric intensivist. A maximum of four punctures was considered for each procedure before changing strategy for patient safety.

In the event of failed cannulation, complication or impossibility of continuing with the assigned technique, vascular access management was left to the treating physician's judgement. Another anatomical site could be attempted, ultrasound-guided technique or anatomical landmark technique could be used, or venous cut-down could be performed. In all cases, the priority was to ensure patient safety and timely central vascular access for treatment.

For the efficacy outcome, the procedure was considered effective if it was achieved within two or fewer attempts and within 20 minutes or less. For the safety/procedural clinical outcome, it was evaluated by absence of serious immediate complications and presence of two or fewer non-serious complications, such as inadvertent internal carotid artery puncture not causing arterial thrombosis, air embolism or vascular injury, and venous or arterial

haematoma at the puncture site not causing internal jugular vein thrombosis, vascular injury, displacement or airway collapse.

15c. Strategies to improve adherence/fidelity to the protocol

To promote fidelity to the protocol, procedures were performed by two paediatric intensivists experienced in CVC placement using the Seldinger technique, both by anatomical landmarks and ultrasound guidance. Both operators had formal training in ultrasound for vascular access and were standardised before study initiation.

Before the trial started, comparability of procedural performance between both operators was assessed by reviewing CVC procedures performed during the previous year. The frequency of successful cannulation and procedure-related complications was compared between operators. No relevant differences in efficacy or safety were identified; therefore, both operators were considered comparable for performing the two trial interventions.

During the study, adherence to the protocol was promoted through use of a data collection form in which the assigned technique, anatomical puncture site, number of attempts, placement time, success or failure of cannulation, complications and any deviation from the assigned procedure were recorded.

Assistant 1 supervised protocol compliance during patient enrolment, informed consent, random allocation and clinical follow-up. Assistant 2 recorded procedural variables and safeguarded the corresponding information. Review of protocol adherence was performed weekly by the assigned collaborators by verifying data collection forms, reviewing selection criteria, confirming the assigned technique and comparing with available clinical records.

Protocol deviations were classified as major or minor. Major deviations were those that could modify study validity or patient safety, including inclusion of a patient who did not meet selection criteria, lack of informed consent before the procedure, performance of a technique different from the assigned technique without clinical justification, absence of essential primary outcome data or loss to follow-up before evaluating efficacy or safety. Minor deviations were those that did not compromise patient safety or primary outcome assessment, such as administrative omissions, delays in recording, correctable errors in the data collection form or non-essential incomplete data that could later be verified in the clinical record.

Each identified deviation was documented in the data collection form or corresponding record, including date, description, classification, probable cause and corrective action. In case of major deviations or events with possible impact on patient safety, these had to be communicated to the principal investigator and, when appropriate, to the institutional ethics or research committee.

15d. Permitted or prohibited concomitant care

All participants received usual care indicated by the Paediatric Intensive Care Unit medical team, regardless of allocated group. Participation in the trial did not modify the comprehensive treatment of the critically ill patient according to care protocols, including ventilatory support, vasoactive drugs, fluid administration, antibiotics, parenteral nutrition, blood products, analgesia, sedation or any other intervention indicated by the clinical condition. No therapeutic intervention required for stabilisation or treatment was prohibited. In the event of complications related to CVC placement, immediate care was provided according to institutional resources and the judgement of the treating team.

16. Outcomes

Complications were classified according to time of onset as immediate, intermediate and late. Immediate complications were those occurring during CVC placement and up to 6 hours after the procedure; intermediate

complications occurred between 7 and 48 hours after the procedure; and late complications occurred from day 3 to day 14 after the procedure.

Primary outcome

The primary outcome was overall efficacy of CVC placement, defined as successful placement of the CVC in the internal jugular vein, confirmed by chest radiography, ultrasound or echocardiography, with a maximum of two attempts and within no more than 20 minutes from the first venous puncture to catheter placement. This was assessed immediately after confirmation of CVC position by radiography or echocardiography.

Overall efficacy was analysed as a dichotomous variable: effective procedure or non-effective procedure. A procedure was considered effective when all of the following criteria were met simultaneously:

1. Successful CVC placement in the internal jugular vein.
2. Confirmation of adequate catheter position by radiography or echocardiography.
3. Cannulation achieved with a maximum of two attempts.
4. Placement time no longer than 20 minutes from the first venous puncture.

For each intervention group, the proportion of effective procedures was reported.

Key secondary outcome

The key secondary outcome was safety of CVC placement. Safety was assessed according to the presence or absence of procedure-related complications.

A procedure was considered safe when no serious immediate complications occurred and, if non-serious complications occurred, these did not exceed two events and did not produce major clinical consequences. Non-serious complications included inadvertent puncture of the internal carotid artery without arterial thrombosis, air embolism or vascular injury, as well as venous or arterial haematoma at the puncture site that did not cause internal jugular vein thrombosis, vascular injury or airway compromise.

Safety was analysed as a dichotomous variable: safe procedure or unsafe procedure. The type, number and timing of complications observed in each group were also described.

Secondary outcomes

- Successful or failed cannulation, defined as adequate or inadequate/not achieved CVC placement, confirmed by radiological, ultrasonographic or echocardiographic control.
- Number of attempts to achieve cannulation, defined as the number of punctures performed with the intention of accessing the internal jugular vein.
- CVC placement time, measured in minutes from the first venous puncture to catheter introduction and placement.
- Cannulation failure, defined as inability to place the CVC in the internal jugular vein using the assigned technique.

Type of complication, including pneumothorax, air embolism, catheter malposition, haemothorax, injury to major vessels, injury to neighbouring structures, cardiac arrest, arrhythmias, haematoma, arterial puncture and catheter-related infection.

Number of complications per intervention, defined as the total number of procedure-related adverse events recorded in each group.

Catheter-related infection, defined according to the clinical and microbiological criteria established in the protocol.

Complications were classified according to time of onset: immediate complications, during CVC placement and up to 6 hours after the procedure; intermediate complications, between 7 and 48 hours after the procedure; and late complications, from day 3 to day 14 after the procedure.

17. Harms / adverse events

Procedure-related adverse events were assessed through active surveillance during CVC placement and subsequent clinical follow-up in the PICU and hospitalisation. Events considered related to CVC placement were mechanical, infectious or clinical adverse events occurring during the procedure or within the defined follow-up period. If a serious complication occurred during the procedure, it had to be reported to the principal investigator and to the local ethics and health research committee.

Complications were classified according to timing: immediate complications, during CVC placement and up to 6 hours after the procedure; intermediate complications, from 7 to 48 hours after the procedure; and late complications, from day 3 to day 14 after the procedure.

The responsible collaborator in the PICU recorded and supervised daily and routinely whether the following complications occurred: pneumothorax, air embolism, catheter malposition, haemothorax, major vessel injury, damage to neighbouring structures, cardiac arrest, arrhythmias, haematoma, arterial puncture, catheter-related infection and CVC duration.

Events were identified through physical examination, clinical monitoring, continuous electrocardiography when indicated, chest radiography, ultrasound, Doppler ultrasound, microbiological cultures or other studies indicated by the treating team. Recording was performed in the data collection form by assigned staff. Subsequently, the information was reviewed in coded form to assess procedural safety and classify events by type, timing and severity. Follow-up of procedure-related adverse events was performed from the beginning of CVC placement until catheter removal, hospital discharge or patient death.

If a complication occurred, the hospital had human and material resources for immediate care, including resuscitation equipment, ventilators, vasoactive drugs, material for pleural drainage, ultrasound, venous cut-down equipment and availability of a paediatric surgeon 24 hours per day.

Severity of complications was defined by the paediatric intensivist on duty and the personnel assigned to follow-up:

Non-serious: arterial puncture without thrombosis, air embolism or vascular injury; haematoma without vascular or airway compromise.

Serious: tension pneumothorax, haemothorax, major vascular injury, cardiac arrest, arrhythmia with haemodynamic compromise, catheter-related infection with systemic reperfusion, death or event prolonging hospitalisation.

18. Participant timeline

Participant involvement began with identification of an eligible patient in the Paediatric Intensive Care Unit, followed by verification of selection criteria, obtaining informed consent from the father, mother or legal guardian and assent from the minor when applicable. Random allocation, the assigned intervention, recording of procedural variables and monitoring of complications during hospital stay were then performed, as shown in Table 1.

Table 1. Schedule of enrolment, intervention, and assessment of participants

Activity / assessment	Screening	Before the procedure	Allocation	Procedure	0–6 hours	7–48 hours	Day 3–14	Follow-up closure
Identification of patient in the PICU with an indication for CVC placement in the internal jugular vein	X							
Verification of eligibility criteria	X							
Informed consent from the father, mother, or legal guardian		X						
Informed assent from the minor, when applicable		X						
Recording of age, sex, weight, and height		X						
Recording of diagnosis, comorbidities, and indication for CVC		X						
Severity assessment using PIM 3 and pSOFA		X						
Simple randomisation by coin toss			X					
Allocation to intervention A or B			X					
CVC placement using the assigned technique				X				
Recording of the anatomical puncture site				X				
Recording of CVC placement time				X				
Recording of the number of punctures or attempts				X				
Assessment of successful or failed cannulation				X				
Confirmation of CVC position by imaging				X				
Monitoring of immediate complications				X	X			
Monitoring of intermediate complications						X		
Monitoring of late complications							X	
Assessment of catheter-related infection							X	X
Recording of CVC duration							X	X
Recording of reason for CVC removal							X	X
Recording of hospital discharge, CVC removal, reason for protocol withdrawal, or follow-up closure								X

Abbreviations: CVC: central venous catheter; PICU: Paediatric Intensive Care Unit; PIM 3: Paediatric Index of Mortality 3; pSOFA: Pediatric

19. Sample size

The sample size calculation was performed before the start of recruitment. It was calculated to compare two independent proportions, corresponding to the expected proportion of successful cannulation between the ultrasound-guided technique and the anatomical landmark technique. The formula for comparison of two proportions with independent groups and 1:1 allocation was used:

$$n = \{ [Z_{\alpha/2} \sqrt{2\bar{p}(1-\bar{p})} + Z_{\beta} \sqrt{p_1(1-p_1) + p_2(1-p_2)}]^2 \} / (p_1 - p_2)^2$$

where p_1 was the expected success proportion with the ultrasound-guided technique, p_2 the expected success proportion with the anatomical landmark technique, $\bar{p}$ the mean of both proportions, $Z_{\alpha/2}$ the value corresponding to a two-sided alpha of 0.05, and Z_{β} the value corresponding to 80% statistical power.

The study by Gallagher RA was used as a reference, reporting a 98% success proportion for ultrasound-guided CVC placement and 79% for the anatomical landmark technique. With $p_1 = 0.98$ for the ultrasound-guided group, $p_2 = 0.79$ for the anatomical landmark group, an expected absolute difference of 0.19, a two-sided significance level of $\alpha = 0.05$ and 80% statistical power ($\beta = 0.20$), a minimum estimated sample size of 43 patients per group was obtained, for a total of 86 participants. The calculation was performed with Epidat version 4.2 using the module for comparison of two independent proportions. The final size was rounded to 49 patients per group; the increase from 43 to 49 per group was conservative, to compensate for possible losses, incomplete data, post-randomisation exclusions or procedures that could not be evaluated.

20. Recruitment

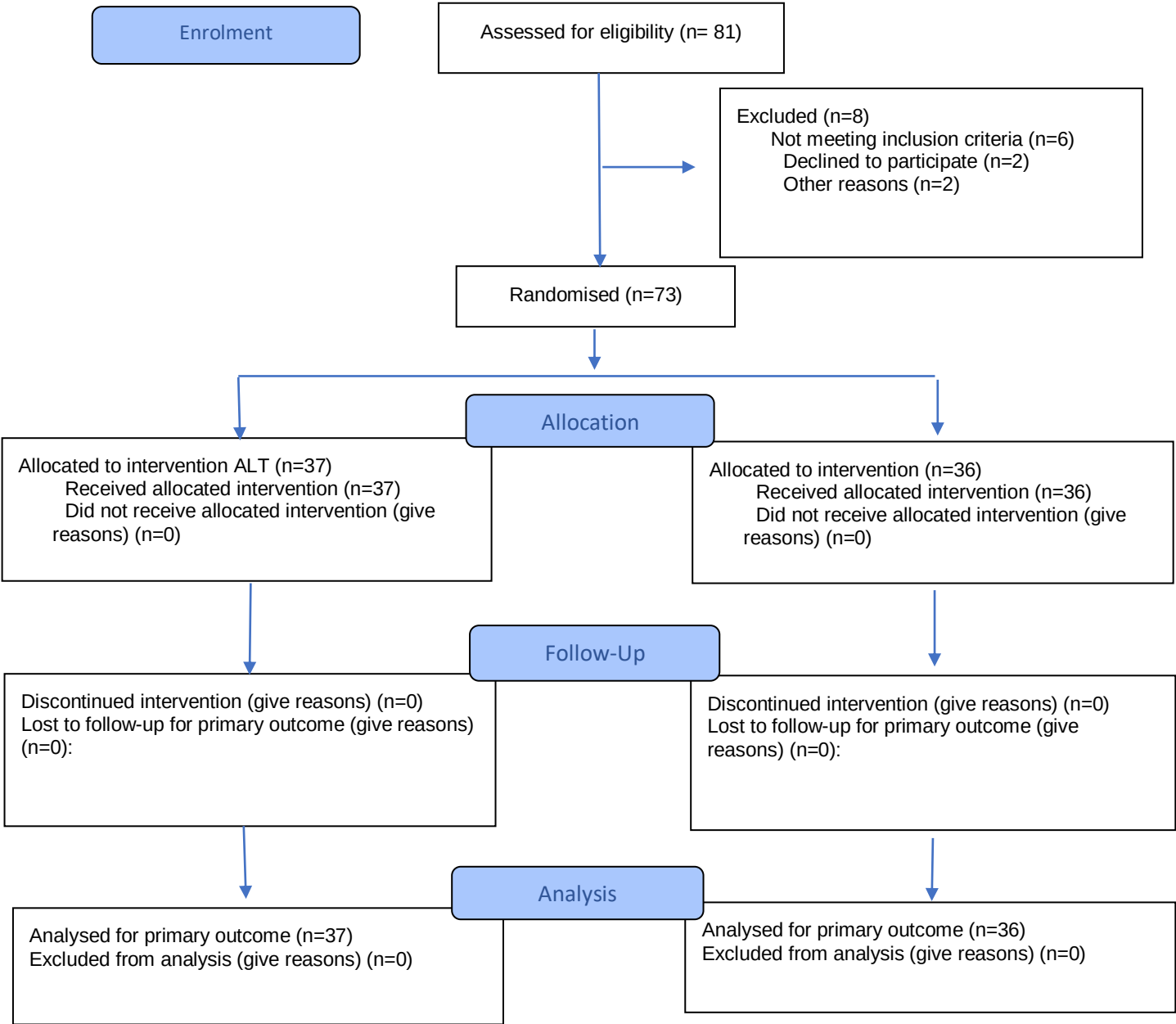
Consecutive sampling of eligible patients was performed. Paediatric patients aged from 1 month to 15 years and 11 months admitted to the Paediatric Intensive Care Unit who required CVC placement in the internal jugular vein as part of their clinical management were assessed for selection.

The responsible physician notified Assistant 1 when a patient met clinical criteria for CVC placement and was potentially eligible for the study. Assistant 1 then went to the PICU, verified selection criteria, contacted the father, mother or legal guardian, explained the study objectives, the interventions being compared, risks, potential benefits, voluntariness of participation and the right to withdraw the patient from the protocol without affecting medical care. After this explanation, written informed consent was requested. In patients aged 8 to 15 years and 11 months who were awake, conscious, not sedated and clinically able to understand the information provided, informed assent was also requested.

The first patient was recruited on 12 September 2019 and the last patient on 5 August 2020. During this period, 81 patients were assessed for eligibility. Of these, 8 patients were not included: 6 did not meet selection criteria and 2 had parents or legal guardians who did not agree to participate in the research protocol. In total, 73 patients were included and randomised: 37 were assigned to the anatomical landmark technique and 36 to the ultrasound-guided technique.

The initially planned sample size was 98 patients, with 49 participants per group. However, recruitment was stopped early after an interim analysis showed that the ultrasound-guided technique had greater efficacy than the anatomical landmark technique. The research team suggested study suspension, and after institutional review of interim results by the research committee, early termination of the protocol was recommended. Therefore, the trial concluded with a total sample of 73 randomised patients.

Figure 1. CONSORT flow diagram showing the recruitment, allocation, follow-up, and analysis of participants.



21. Randomisation: sequence generation

21a. Generation method

Allocation was generated by simple non-computerised randomisation at the time of the procedure, using a coin toss. Assistant 1 performed random allocation and communicated the result to the operator responsible for the procedure.

21b. Type of randomisation

Participants were assigned in a 1:1 ratio to one of two interventions. When the coin landed on the obverse side (heads), the participant was assigned to intervention A, ultrasound-guided CVC placement. When it landed on the reverse side (tails), the participant was assigned to intervention B, CVC placement using the anatomical landmark technique.

No randomisation blocks or stratification by age, weight, clinical severity, operator, side of puncture, anatomical site or other variables were used. This reflected a simple randomisation scheme suitable for the operational feasibility of the procedure in the Paediatric Intensive Care Unit. However, it is recognised that the absence of blocks or stratification may have limited balance between groups in some relevant clinical or procedural variables; these characteristics were described and compared between groups during statistical analysis. The investigator responsible for analysis did not participate in generation of allocation.

22. Allocation concealment mechanism

Allocation was performed immediately before the procedure by simple non-computerised randomisation using a coin toss. Because allocation was generated at the time of the procedure, there was no predetermined random list or sequence. This is recognised as a methodological limitation of the trial because it may have increased the risk of selection bias compared with formal allocation concealment methods.

Nevertheless, to reduce the possibility of directed selection of the intervention group, allocation was performed only after confirming participant eligibility and obtaining informed consent from the father, mother or legal guardian. The result of the coin toss was communicated to the operator responsible for the procedure immediately before CVC placement.

23. Implementation

The paediatric intensivist responsible for clinical care identified potentially eligible patients requiring CVC placement in the internal jugular vein during their stay in the Paediatric Intensive Care Unit and notified Assistant 1.

Assistant 1 verified compliance with selection criteria, including inclusion and exclusion criteria, before initiating any study-related procedure. Once eligibility was confirmed, Assistant 1 contacted the father, mother or legal guardian, explained the study objectives, the interventions being compared, risks, potential benefits, voluntary participation and the right to withdraw the patient from the protocol without affecting medical care. Assistant 1 then obtained written informed consent from the father, mother or legal guardian. In patients aged 8 to 15 years and 11 months who were awake, conscious, not sedated and clinically able to understand the information provided, Assistant 1 also requested assent from the minor.

After confirming eligibility and obtaining informed consent, and assent when applicable, Assistant 1 performed allocation by simple non-computerised randomisation using a coin toss. "Heads" assigned the participant to the ultrasound-guided technique, while "tails" assigned the participant to the anatomical landmark technique.

Once allocation had been performed, Assistant 1 communicated the assigned technique to the operator responsible for the procedure immediately before CVC placement. Operators were paediatric intensivists previously trained and standardised in both techniques.

During the procedure, collaborating staff recorded data in the data collection form, including assigned technique, anatomical site, number of attempts, placement time, success or failure of cannulation and

immediate complications. Subsequently, intermediate and late complication follow-up was performed by assigned personnel according to the protocol timeline.

24. Blinding

24a. Who was blinded

Because of the nature of the procedure, the operator performing CVC placement could not be blinded. The personnel present during the intervention could not be blinded either.

The outcome assessor performed the main assessment with coded groups. Subsequent review by Assistant 1 was administrative and intended to verify data consistency and did not modify the main blinded assessment. The principal investigator remained blinded to group identity during statistical analysis.

24b and 24c. How blinding was achieved

The trial was considered single-blind. Because of the nature of the procedure, neither the operator performing CVC placement nor the clinical team present during the intervention could be blinded. Personnel recording directly observed variables during CVC placement could not be blinded to the intervention group, because they had to document the technique used, anatomical site, number of attempts, placement time and immediate complications. However, after the procedure, information was coded in an electronic database, identifying groups using non-revealing codes. Assessment of efficacy and safety outcomes was performed with coded information by an outcome assessor blinded to intervention group. Likewise, the principal investigator, who performed and supervised statistical analysis, remained blinded to group identity during the main analysis. Therefore, blinding applied to the outcome assessor and to the principal investigator performing statistical analysis.

24c. Unblinding

As operators were not blinded because of the nature of the interventions, no unblinding procedure was required for them. For the principal investigator, group identity was to be revealed only after database closure and completion of the main statistical analysis, unless required for safety reasons or review by the ethics or research committee. During the protocol, an analysis was performed after completing 50% of the sample. When a trend in favour of one technique was observed, a second analysis was performed at 74% of the sample, showing greater efficacy with technique A. The results were submitted for assessment by the research committee, and the clinical trial was terminated.

25. Data collection methods

25a. Assessment and data collection

Data were collected using a data collection form designed specifically for the protocol. Information was obtained from direct observation of the procedure, clinical records, available imaging studies and microbiological results when applicable.

Demographic and anthropometric variables were recorded, including protocol identification number, age, sex, weight, height and body surface area. Clinical variables were also recorded, including dates of admission and discharge, admission diagnosis, discharge diagnosis, comorbidities, clinical indication for CVC placement, PIM 3 and pSOFA at the time of the procedure.

Procedure-related variables included assigned technique, anatomical puncture site, date of CVC placement, placement time, number of punctures or attempts, problems during the procedure, successful or failed

cannulation, confirmation of catheter position by imaging, operator professional qualification and need to change anatomical site.

Follow-up variables included immediate, intermediate and late complications, type and number of complications, catheter-related infection, CVC duration, cause of catheter removal, reason for exiting the protocol and patient status at follow-up closure.

During the procedure, Assistant 1 (assigned personnel) recorded directly observed variables in the data collection form. Complementary clinical data were obtained from the medical record. Patient severity was assessed using PIM 3 and pSOFA at the time of CVC placement.

To ensure data quality, an assigned collaborator performed a second verification of recorded data, comparing the data collection form with the clinical record, imaging reports and available records. In case of inconsistencies or incomplete data, the information was reviewed again in the clinical record before being considered missing for analysis.

25b. Retention and follow-up

Patients were followed during their stay in the Paediatric Intensive Care Unit and subsequently during hospitalisation, in order to identify complications related to CVC placement and during its use.

Follow-up for procedure-related events was performed from the start of CVC placement until catheter removal, hospital discharge or patient death, if applicable.

During follow-up, immediate, intermediate and late complications, catheter-related infection, CVC duration and cause of removal were recorded. In the event of voluntary withdrawal, transfer to another unit, voluntary discharge, incomplete clinical record or inability to complete follow-up, the reason for leaving the protocol was documented.

No losses to follow-up were reported in this study. All randomised patients had data available for assessment of the main outcomes. Recorded information underwent double verification by an assigned collaborator before final integration of the database.

26. Data management

Information recorded in the data collection form was entered by a collaborating investigator into a coded electronic database protected by password. Each participant was identified by a unique protocol number to protect confidentiality and avoid use of direct personal identifiers in the database.

The database included demographic, clinical and procedural variables, as well as efficacy and safety outcomes, CVC placement-related complications, catheter duration and cause of removal. For statistical analysis, the database did not include names, social security numbers, medical record numbers or other direct identifiers.

The linkage list between the protocol number and participant identity was stored in a file separate from the database, password-protected and accessible only to personnel authorised by the research team. This list was kept exclusively for verification, data clarification and follow-up traceability, and was not used during statistical analysis.

Data entry was performed by a collaborating investigator. Subsequently, a second collaborator verified entered information by comparison with the data collection form, clinical record and available source documents. If inconsistencies, omissions or entry errors were identified, these were reviewed in the original sources before correction. Any relevant modification in the database was documented in a change log, including date, modified variable, reason for correction and person responsible for the change.

The electronic database file was stored on an institutional computer or authorised device, password-protected and with access restricted to the authorised research team. Periodic backups of the database were made in a secure medium, also password-protected, to prevent information loss. Access to the database, backups and code-identity linkage list was limited to authorised personnel.

Source documents and data collection forms were kept in the Paediatric Intensive Care Unit headquarters under institutional confidentiality measures. Physical access to these documents was restricted to authorised research team personnel.

Data were used exclusively for research and statistical analysis. The coded database and related documents will be kept for up to seven years in accordance with applicable institutional guidelines. If the database is shared or published, it will first be anonymised by removing direct and indirect identifiers that could allow participant identification. Data availability will be subject to current institutional regulations, corresponding authorisations, and principles of confidentiality and personal data protection.

27. Statistical methods

27a. Group comparison for primary and secondary outcomes

Qualitative variables were described using frequencies and percentages. Quantitative variables were described using mean and standard deviation when normally distributed, or median and interquartile range when not normally distributed. Between-group comparisons used the chi-squared test or Fisher exact test for nominal variables. For quantitative variables, Student t test or Mann-Whitney U test was used according to data distribution. To estimate the risk associated with complications according to technique used, relative risk with 95% confidence intervals was calculated. To assess clinical impact, the number needed to treat was calculated when applicable. Statistical significance was set at $p < 0.05$. Analysis was performed with IBM SPSS Statistics Version 31.0.0.0 (117) and Epidat 3.1. Epidemiological calculations were verified with Epidat 4.2.

27b. Population included in each analysis

The main analysis, based on available cases admitted to the PICU during the study period, was performed according to the superiority framework of the trial, comparing outcomes between the group assigned to the ultrasound-guided technique and the group assigned to the anatomical landmark technique. Randomised participants with complete and verifiable procedural and primary outcome data were included. Because the original protocol did not formally specify an intention-to-treat analysis, results were analysed mainly based on cases available for the primary outcome. When deviations from the assigned procedure occurred, these were documented and considered in complementary analyses. In addition, a per-protocol analysis was performed, including only procedures performed according to the assigned technique and without major protocol deviations. This analysis was considered complementary and aimed to explore the consistency of results observed in the main analysis.

27c. Handling of missing data

Missing data were identified through review of the data collection form and clinical record. When a variable was not recorded in the data collection form, original sources were checked, including medical record, procedure notes, nursing records, imaging studies and laboratory or microbiology reports, as applicable. Analyses used only available, verified data from original sources. No statistical imputation of missing data was performed. No missing data were identified for variables corresponding to the primary outcome or main procedural outcomes. If missing data existed in secondary or descriptive variables, these were explicitly reported and the corresponding analysis was performed using cases available for each variable.

27d. Additional analyses

Additional exploratory subgroup analyses were performed by age and weight, in order to assess whether the magnitude of effect of the ultrasound-guided technique varied according to clinically relevant paediatric patient characteristics. These analyses were not considered confirmatory and were interpreted as hypothesis-generating. No formal adjustment for multiplicity was performed for secondary outcomes or subgroup analyses because of their exploratory nature. Therefore, p values derived from these analyses were interpreted with caution, considering direction and magnitude of effect, 95% confidence intervals and clinical plausibility of findings.

28. Data monitoring committee

28a. Committee composition

No independent Data Monitoring Committee was established because this was a single-centre randomised clinical trial with limited sample size, a procedural intervention routinely used in the PICU and in-hospital follow-up. Participant safety was supervised by the clinical team and investigators of the Paediatric Intensive Care Unit and by the investigators responsible for the protocol.

Complications related to CVC placement were treated immediately by the treating team, with available human and material resources for resolution of adverse events.

28b. Interim analyses and stopping guidelines

Two analyses were planned during the study: one at 50% of the sample and one after completing 100% of the sample. Data were delivered to the principal investigator for blinded statistical analysis. According to results of the first analysis, investigators could consider performing an interim analysis before completing the total sample.

Stopping criteria: the internal analysis was performed by the investigator responsible for statistical analysis using a coded database. Results were reviewed by the research team and, in the presence of a clinically relevant difference in favour of one technique, the decision for early stopping was submitted for institutional review by the corresponding ethics and/or research committee. The study could be stopped or modified if a clear efficacy advantage of one technique was identified, an unexpected increase in serious complications occurred, the ethics or research committee recommended it, or the research team reached a unanimous decision in response to an unforeseen risk for participants. No formal statistical early-stopping rule such as O'Brien-Fleming, Pocock or Haybittle-Peto was used. The early-stopping decision was based on the magnitude of the observed effect, the clinical relevance of the primary outcome and ethical considerations. The absence of a formal early-stopping rule is recognised as a methodological limitation of the study.

29. Trial monitoring

Trial monitoring was performed by the research team throughout study conduct. Because this was a single-centre clinical trial with limited sample size, in-hospital follow-up and no external funding, there was no independent external monitoring. Assistant 1 supervised patient enrolment into the protocol, verified compliance with inclusion and exclusion criteria, confirmed obtaining informed consent and assent when applicable, supervised correct implementation of the randomisation procedure and followed complications related to CVC placement. Assistant 2 recorded clinical and procedural variables in the data collection form, verified completeness of recorded information, identified possible missing data or inconsistencies, and safeguarded study documentation and each participant's information. The principal investigator supervised overall data quality, verified consistency of the coded database and performed the final statistical analysis. Recorded information was reviewed weekly by the responsible collaborators. During these reviews, the following were verified: participant eligibility, informed consent, correct assignment to the corresponding intervention, compliance with the assigned technique, occurrence of complications and adverse events,

presence of missing or inconsistent data, and possible protocol deviations. Identified deviations were documented in the data collection form and reviewed by the research team to determine their potential impact on participant safety or validity of trial results. Clinical follow-up of participants was also performed during hospital stay for identification and recording of immediate, intermediate and late procedure-related complications.

30. Research ethics approval

The protocol was submitted to and approved by the Local Health Research Ethics Committee and the Local Health Research Committee of UMAE No. 48, Gynecology-Pediatrics Hospital, Mexican Social Security Institute, before recruitment began (see appendices).

According to Article 17 of the Regulations of the General Health Law on Health Research, the study was classified as research involving greater than minimal risk. Because participants were critically ill paediatric patients, they were considered a vulnerable population. All procedures complied with national ethical standards, the Regulations of the General Health Law on Health Research, the Declaration of Helsinki and its amendments, the Nuremberg Code and current Good Clinical Practice.

Informed consent was obtained from the father, mother or legal guardian before patient inclusion. In patients aged 8 to 15 years and 11 months who were awake, conscious, not sedated and clinically able to understand the information, written assent was also obtained. Participation was voluntary, and refusal to participate or withdrawal from the study did not affect the patient's medical care.

The protocol was approved by the ethics committee on 12 June 2019 and by the research committee on 20 June 2019, with registration number R-2019-1002-028. Approval letters from the ethics and research committees are attached. Any substantial modification to the protocol had to be submitted for review and approval by the Local Health Research Ethics Committee and Local Health Research Committee before implementation. This included changes to objectives, selection criteria, interventions, outcomes, sample size, consent procedures, follow-up, statistical analysis or any aspect that could modify participant risk or methodological validity.

If an urgent modification was required for participant safety, it could be implemented immediately to protect the patient, with justification documented and subsequently reported to the Local Ethics Committee and Local Research Committee for review. Once the trial is registered in ISRCTN, any substantial post-registration modification will be communicated and updated on the platform to maintain public traceability of the protocol. Study information will be updated after trial registration is obtained.

The trial was registered retrospectively because, although the protocol had been approved by the Local Health Research Ethics Committee and the Local Health Research Committee before recruitment began, international public registration was not completed before enrolment of the first participant. The study was initially developed as a locally approved academic and institutional protocol. Subsequently, during preparation for scientific dissemination and publication, the need to register the trial in a recognised international platform was identified. Objectives, selection criteria, interventions, outcomes, sample size and statistical analysis plan were defined before recruitment began and were not modified based on results. Retrospective registration was performed to promote transparency, study traceability and public availability of the protocol.

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