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Application of point-of-care ultrasound-guided tip navigation combined with visualised directional high-frequency linear array probe compression to improve the success rate of umbilical venous catheterisation in critical neonates: protocol of a multicentre randomised controlled trial in neonatal units

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ABSTRACT

Introduction Conventional umbilical venous catheterisation (UVC) relies on 'blind' insertion without ultrasound guidance, resulting in low success and high complication rates. While point-of-care ultrasound (POCUS)-based tip navigation and location has improved this scenario by enabling real-time visualisation of the catheter tip during UVC, challenges remain when the catheter is inadvertently inserted into an incorrect vessel. Selecting effective intervention methods to correct the catheter direction has become a key research focus. This study aims to evaluate the safety and efficacy of a novel technique combining POCUS-guided tip navigation with visualised directional high-frequency linear array probe compression (P-TN+vdHLAP C). This technique is expected to become a standardised protocol for POCUS-guided UVC, improving catheterisation success rates, minimising the frequency of insertion attempts and reducing catheterisation time.

Methods and analysis This prospective, multicentre, single-blind, superiority, 1:1 parallel, randomised controlled trial will recruit 100 infants who have failed the initial UVC attempt using the conventional method. Participants will be randomly assigned to either the intervention group receiving P-TN+vdHLAP C or the control group receiving POCUS-guided tip location. The primary outcome measure is the success rate of UVC, defined as the proportion of catheter placements that are successfully positioned at the entrance of the inferior vena cava into the right atrium, as confirmed by POCUS. Secondary outcomes include UVC procedure time, total number of catheter insertions and postoperative monitoring indicators such as catheter tip location, incidence of complications and umbilical catheter indwelling time. Outcome measures will be assessed at seven time points: immediately after catheter placement, 12 hours, 24 hours, 48 hours and 7 days postplacement, catheter removal and discharge. Data analysis will be conducted using R (V.4.3.2).

Ethics and dissemination The study protocol has been approved by the ethics committee of Fujian Children's Hospital (protocol number 2024ETKLRK09019). Prior to enrolment, written informed consent will be obtained from the legal guardians of all participants by the study staff. On completion of the trial, the results will be submitted for peer-reviewed publication in an international scientific journal.

Trial registration number ChiCTR2400090737.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective, multicentre, randomised controlled trial design ensures robust evaluation of the intervention.
⇒ Multicentre approach allows for diverse participant recruitment and enhances generalisability.
⇒ Standardised training and standard operating procedures ensure consistent application of techniques across centres.
⇒ Advanced ultrasound proficiency required may limit widespread adoption of the technique.
⇒ Lack of specific inclusion criteria for gestational age and birth weight may affect result interpretation.

INTRODUCTION

Background and rationale

Umbilical venous catheterisation (UVC) has a history of over 70 years since it was first

reported in 1951 for neonatal exchange transfusion.[1] UVC has emerged as one of the most widely used central venous access procedures in infants during the initial days following birth due to the broad diameter of the umbilical vein, simple operation, extended indwelling time of 10–14 days and relatively low incidence of complications when performed under ultrasound guidance.[2] UVC can provide immediate and safe vascular access[3] and can be performed for small for gestational age and low birthweight infants; those who require advanced life support procedures such as tracheal intubation and volume expansion, which requires rapid and multiroute or hypertonic drug infusion; as well as for infants with a history of multiple failed peripheral venipunctures. Currently, UVC is frequently used for central venous pressure measurement, emergency intravenous infusion, exchange transfusion and long-term parenteral nutrition in extremely low birth weight infants.[4] Additionally, the procedure has occasionally been employed as a reinfusion pathway for venovenous extracorporeal membrane oxygenation,[5] temporary pacemaker implantation in infants with congenital complete atrioventricular block[6] and for various interventional procedures, including ductus arteriosus occlusion, balloon pulmonary valvuloplasty and balloon atrial septostomy.[7]

In the conventional method of UVC, the practitioner estimates the insertion depth of the umbilical catheter prior to insertion, based on surface positioning measurement, nomogram, weight estimation and other techniques.[8] The umbilical catheter is then 'blindly' inserted to the predicted depth, relying solely on the practitioner's expertise without any navigational assistance. Following successful aspiration of venous blood after connecting the umbilical catheter to a 10 mL syringe filled with 0.9% sodium chloride, the catheter can be securely fixed. Subsequently, bedside anteroposterior and lateral thoracoabdominal radiographic images are obtained to determine the position of the tip of the umbilical catheter. The optimal location of the tip is typically 0.5–1 cm above the diaphragm or at the level of the ninth thoracic vertebra.[9] If the catheter is improperly positioned, repeated adjustments and multiple radiographic scans will be necessary.

The success rate of the conventional method of UVC ranges from 23% to 54%,[10] and the procedure is associated with a high incidence of complications.[11] One of the most prevalent complications is ectopic catheter position due to migration or malposition, which can lead to further complications such as arrhythmia, pericardial tamponade,[12] liver abscess/haematoma, liver necrosis and ascites.[13] Other complications include catheter-related thrombosis,[14] bloodstream infection,[15] neonatal necrotising enterocolitis,[16] venobiliary fistula,[17] umbilical vein perforation[18] and diffuse ischaemic injury of the extremities.[19] Although the conventional method of UVC is considered outdated, it remains the most commonly used approach in many countries, particularly in those where bedside ultrasonography is not widely available.

Ectopic umbilical catheter placement or endothelial injury resulting from repeated catheter insertion is the primary cause of most UVC-related complications.[20 21] Therefore, it is crucial to optimise the success rate of UVC, minimise the frequency of repeated catheter insertion during the procedure and ensure minimal migration of the catheter from its intended position during use.

The Point-of-Care Ultrasound (POCUS) Working Group of the European Society of Paediatric and Neonatal Intensive Care issued international evidence-based guidelines on POCUS for critically ill newborns and children in 2020,[22] representing a significant advancement in the utilisation of POCUS within the neonatal intensive care unit (NICU). The guidelines advocate for neonatologists to employ POCUS to localise the tip of the umbilical catheter during UVC.

Thus far, studies applying POCUS for UVC have focused on tip localisation and tip navigation.[23] Tip localisation enables precise determination of the position of the umbilical catheter tip during UVC. The limitation lies in the inability to determine the type and cause of umbilical catheter malposition if the catheter tip is not found in the target position. In such cases, the only recourse is to repeatedly probe the umbilical catheter by retracting and reinserting it until the catheter tip enters the ultrasound field of view at the target location. This approach significantly increases the number of insertion attempts, catheterisation time, failure rate, as well as complications such as thrombosis. Unlike tip localisation, tip navigation using POCUS enables real-time visualisation of the movement of the umbilical catheter tip during UVC. This not only confirms whether the tip of the umbilical catheter has entered the target position but also analyses the causes of UVC failure through POCUS-based catheter tip tracking, such as the catheter entering an abnormal route or undergoing backfolding. In recent years, numerous clinical studies have confirmed the feasibility and accuracy of POCUS-based tip localisation and tip navigation during UVC in infants.[10 24] Moreover, structured programmes such as Neo-ECHOTIP[25] and Safe Insertion of Umbilical Venous Catheters (SIUVeC)[26] have been developed to facilitate the widespread adoption of these POCUS-based techniques across various scenarios, while also making them easily teachable and learnable.

Nevertheless, POCUS-based tip navigation only allows for the real-time visualisation of the umbilical catheter tip during the UVC procedure. When the umbilical catheter enters into an incorrect vessel under POCUS guidance, selecting effective intervention methods to correct the direction of the umbilical catheter has become a research focus in current times. In such cases, common intervention methods reported in the literature include manual mobilisation of the posterior aspect of the liver,[27] applying pressure to the right upper abdomen, positioning the infant in a right lateral decubitus position[28] and using the double catheter technique.[29] While these approaches have been shown to reduce the rate of UVC failure by 50%,[10] they are empirical, tentative and non-directional.

Kishigami *et al* conducted a study that initially reported the successful performance of UVC through the ductus venosus. This was achieved by compressing the upper abdomen near the portal sinus of the liver to align the umbilical vein and ductus venosus under ultrasound guidance.[10] This represents the initial implementation of POCUS-based visualised directional UVC tip navigation. However, our previous study revealed an angle between the sagittal sinus of the left branch of the hepatic portal vein and the ductus venosus in both the sagittal and transverse views of the liver, both anatomically[30 31] and as observed using ultrasound examination.[32] Hence, by compressing the upper abdomen close to the hepatic portal vein, the umbilical vein and ductus venosus can merely be aligned in the sagittal view of the liver. It is not possible to adjust the angle on the transverse view, which may lead to UVC failure.

Therefore, our study proposes the concept of 'POCUS-guided tip navigation combined with visualised directional high-frequency linear array probe compression (P-TN+vdHLAP C)'. This technique involves using POCUS-based tip navigation during UVC. If the umbilical catheter enters an incorrect vessel, the practitioner is instructed to slowly retract the catheter to the left branch of the portal vein sagittal sinus, and then use visualised directional high-frequency linear array probe compression technology. Specifically, the ultrasound probe is positioned above the incorrect vessel such that its long axis is clearly displayed in the middle of the screen. The probe is then applied to the blood vessel with slow and even pressure until significant collapse of the vessel is observed, preventing further entry of the umbilical catheter into the incorrect vascular route. Subsequently, continued slow delivery of the catheter will ensure successful placement at the target position.

Objective

The aim of this study is to determine the safety and efficacy of the P-TN+vdHLAP C protocol of UVC. This technique is anticipated to be established as a standardised protocol for POCUS-guided UVC in infants, ultimately achieving the objective of improving the success rate of catheterisation, reducing catheterisation time and frequency of insertion, which holds promising application prospects and warrants further clinical research and promotion.

Hypothesis

The P-TN+vdHLAP C protocol can significantly enhance the success rate of UVC, reduce catheterisation time, minimise the number of insertions and lower the risk of complications when compared with conventional 'POCUS-guided tip location (P-TL)'.

Trial design

This is an investigator-initiated, prospective, multicentre, single-blind, superiority, 1:1 parallel, randomised controlled trial. After conducting baseline assessments, which include sociodemographic information, disease characteristics and POCUS-based measurement of ultrasound parameters of vessels involved in the UVC pathway, we will randomly assign eligible participants in a 1:1 ratio to undergo UVC via either the P-TN+vdHLAP C or P-TL protocol. A flow chart of the study is shown in figure 1.

METHODS AND ANALYSIS

Study setting

This study is scheduled to be conducted from 1 September 2024 to 1 September 2025, within the 40-bed tertiary NICUs of 3 hospitals: Fujian Children's Hospital, Fujian Provincial Maternity and Children's Hospital, and Fujian Obstetrics and Gynecology Hospital. The planned recruitment period is scheduled from 14 October 2024 to 31 August 2025.

Eligibility criteria

The participants of this study will be newborns admitted to the NICU within 72 hours of birth. The inclusion criteria are as follows:

1. Critically ill newborns requiring prompt establishment of intravenous access and emergency intravenous infusion.
2. Very/extremely low birthweight infants requiring prolonged central venous infusion.
3. Critically ill newborns in need of central venous pressure monitoring.
4. Newborns requiring exchange or partial exchange blood transfusion.

The exclusion criteria are as follows:

1. Umbilical cord infection.
2. Necrotising enterocolitis.
3. Peritonitis.
4. Damage to local blood vessels in the lower limbs or buttocks.
5. Abnormal development of umbilical blood vessels and/or hepatic blood vessels.
6. Severe heart malformations.
7. Discharge from the hospital against medical advice within 7 days of admission, at the request of the patient's guardian.

The 2 POCUS implementers in this study are neonatologists with over 10 years of clinical experience and over 5 years of experience in neonatal critical care ultrasonography. Both have acquired the exclusive certificate issued by the Chinese Critical Care Ultrasound Study Group and possess the qualifications required for critical care ultrasound evaluation. The ultrasound physician responsible for POCUS quality control has over 10 years of clinical ultrasound experience and over 5 years of neonatal ultrasound experience. Finally, the study will include 2 UVC practitioners, who are neonatologists with over 3 years of experience in neonatal clinical work and are proficient in various commonly performed neonatal procedures.

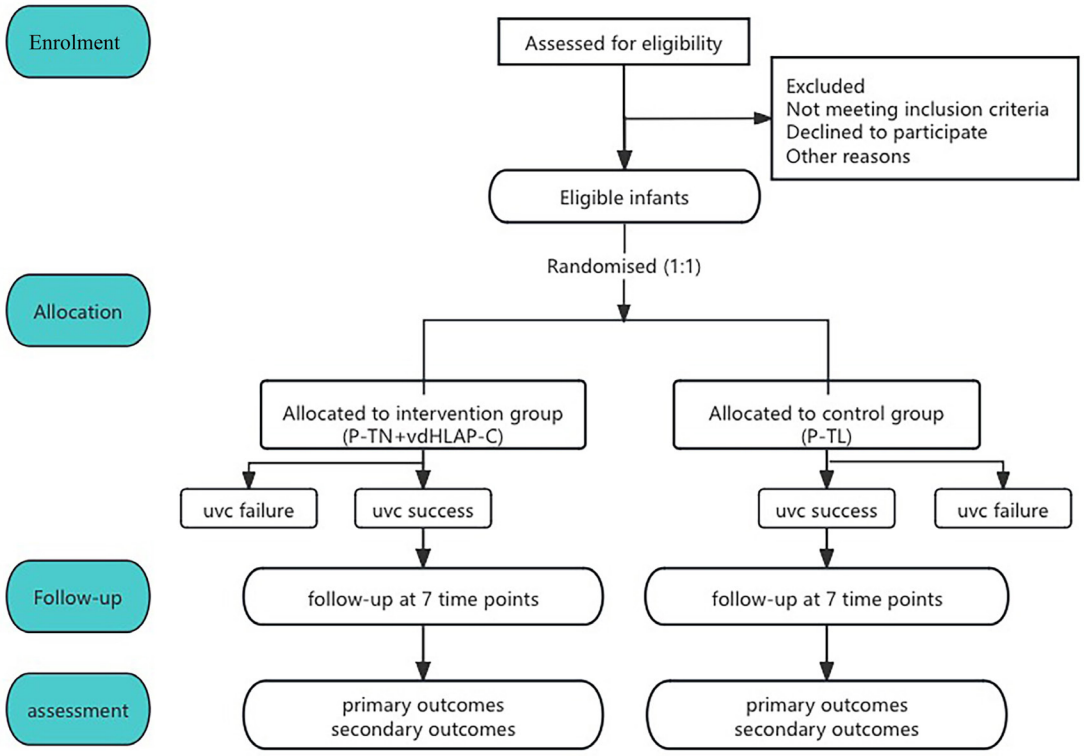

Figure 1 Study design and timeline of the procedures. P-TL, point-of-care ultrasound-guided tip location; P-TN+vdHLAP C, point-of-care ultrasound-guided tip navigation with visualised directional high-frequency linear array probe compression; UVC, umbilical venous catheterisation.

Interventions

(1) Preoperative assessment for UVC: We will use the ultrasound diagnostic device manufactured by the Philips Ultrasound (Bothell, Washington, USA), featuring the model number CX50 and the L12-3 high-frequency linear array probe. The POCUS implementers are designated to perform the ultrasound number encoding, POCUS-based measurements of the ultrasound parameters of the vessels involved in the UVC pathway, and image archiving for all the study subjects. The ultrasound physician is then tasked with interpreting the images and re-examining the parameters for quality control to guarantee the accuracy of the evaluation.

Prior to the commencement of the study, the two POCUS implementers and the ultrasound physician conducted a comprehensive review of the protocol for pre-UVC POCUS assessment. Under the guidance of the ultrasound physician, the POCUS implementers underwent 14 working days of training, averaging 8 hours per day. The duration allocated for pre-UVC POCUS assessment was established at 10 min, as determined by the ultrasound physician and validated by both POCUS implementers. It is important to note that this 10 min time frame encompassed tasks such as ultrasound number encoding, image acquisition, data measurement and archiving. Finally, we optimised our procedures so that once the POCUS implementer completed number encoding and image acquisition, the UVC practitioner could initiate the UVC procedure while allowing the POCUS implementer to continue with data measurement and archiving at bedside. This adjustment effectively reduced the pre-UVC POCUS assessment time to between 3 and 5 min without compromising either assessment quality or delaying subsequent UVC catheterisation.

(2) The UVC procedure: One of the UVC practitioners will use a precise formula to calculate the estimated depth of umbilical catheter insertion. They will opt for the 3.5-Fr single-lumen umbilical catheter manufactured by Utah Medical Products (Midvale, Utah, USA). The specific operational process is derived from the description of the UVC procedure in the textbook for Chinese neonatologists: *Practice of Neonatology*.[33] The surface of the ultrasound probe will be smeared with a coupling agent and then covered with a disposable sterile probe cover, which is to be tightened with a rubber band. The surface of the probe will be smeared with the sterile coupling agent once again. The long-axis section of the inferior vena cava will be displayed under the probe, revealing the entrance of the inferior vena cava into the right atrium. The probe will be held in this position without moving. The UVC practitioner will slowly insert the umbilical catheter to the insertion depth estimated by the POCUS implementer. If the tip of the umbilical catheter is observed at the entrance of the inferior vena cava into the right atrium, the procedure will be categorised as one-time UVC success; if the catheter tip is not seen at the entrance of the inferior vena cava into the right atrium, the procedure will be recorded as one-time UVC failure,

and POCUS will be immediately conducted to determine the direction of the umbilical catheter.

(3) Grouping process and corresponding interventions: All subjects with one-time UVC failure will be randomly assigned to the intervention group or the control group. During the UVC procedure, the subjects in the intervention group will receive P-TN+vdHLAP C, while those in the control group will receive P-TL.

(4) Standard protocol for the intervention group: Under ultrasound monitoring, the UVC practitioner is instructed by the POCUS implementer to gradually insert the umbilical catheter into the sagittal sinus of the left branch of the portal vein. Under ultrasound monitoring, the umbilical catheter can be visualised passing through the sagittal sinus of the left branch of the portal vein, into the ductus venosus, and then reaching the entrance of the inferior vena cava into the right atrium. If the umbilical catheter is successfully placed to the estimated insertion depth in one attempt, fine-tuning will be carried out based on the tip location indicated by POCUS to ensure that the tip of the umbilical catheter has reached the entrance of the inferior vena cava into the right atrium. The subsequent steps will be continued in accordance with the UVC procedure. If the umbilical catheter is found to enter an abnormal route or undergo backfolding during UVC, the practitioner is instructed to slowly withdraw the umbilical catheter to the sagittal sinus of the left branch of the portal vein first. The practitioner is instructed to then continue to slowly insert the umbilical catheter until it is successfully delivered to the target position by employing the P-TN+vdHLAP C technique. This scenario is to be categorised as non-one-time UVC success.

P-TN+vdHLAP C protocol: The high-frequency linear array probe should be precisely positioned directly above the blood vessel, which is the incorrect path that the umbilical catheter ought not to enter, and the long axis of the blood vessel should be distinctly displayed in the middle of the screen. The high-frequency linear array probe will then be applied to the blood vessel with slow and even pressure until significant vascular collapse is observed, preventing the erroneous insertion of the umbilical catheter into the blood vessel. For instance, if the umbilical catheter is repeatedly and mistakenly inserted into the transverse part of the left branch of the portal vein, the high-frequency linear array probe will be precisely positioned above the transverse part of the left branch of the portal vein to clearly exhibit its long axis, and pressure will be exerted on the ultrasound probe to cause a conspicuous collapse of the blood vessel, thereby preventing the reinsertion of the umbilical catheter at this location (figures 2–5).

If the target position cannot be reached after five attempts using the P-TN+vdHLAP C technique, the procedure will be recorded as UVC failure. For those with UVC failure in the intervention group, the P-TL technique will be attempted. The procedure will be marked as final UVC success if the umbilical catheter reaches the target position within 3 attempts using the P-TL method. Otherwise, the procedure will be recorded as final UVC failure.

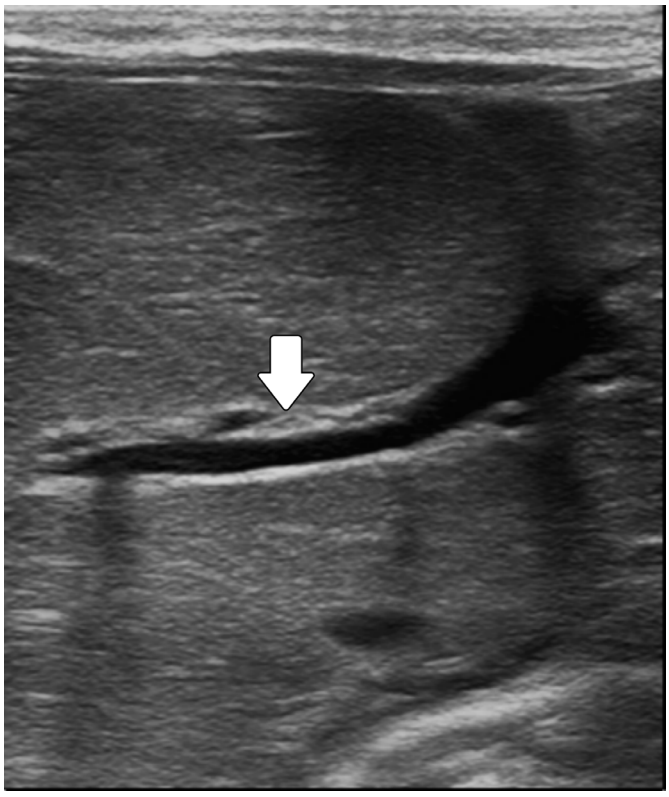

Figure 2 Transverse section of the left branch of the portal vein (prior to P-TN+vdHLAP C). P-TN+vdHLAP C, point-of-care ultrasound-guided tip navigation with visualised directional high-frequency linear array probe compression.

(5) Standard protocol for the control group: The long-axis section of the inferior vena cava will be displayed under the probe by the POCUS implementer, revealing the entrance of the inferior vena cava into the right atrium. The probe will be held in this position without moving. The practitioner is instructed to withdraw the umbilical catheter by 3–4 cm (approximately at the position of the sagittal sinus of the left branch of the portal vein). The umbilical catheter will be delivered slowly, while conventional external adjunctive operations such as manual compression of the right upper quadrant of the abdomen, manual mobilisation of the posterior aspect of the liver and placement of the patient in the right lateral decubitus position will be performed until the entry of the umbilical catheter is observed at the target location within the field of view of the probe. This scenario is defined as non-one-time UVC success. If the target position cannot be reached after five attempts using the P-TL technique, the procedure will be marked as UVC failure. For those with UVC failure in the control group, the P-TN+vdHLAP C technique will be attempted. If the umbilical catheter reaches the target position within three attempts using the P-TN+vdHLAP C method, the procedure will be categorised as final UVC success. Otherwise, it will be categorised as final UVC failure.

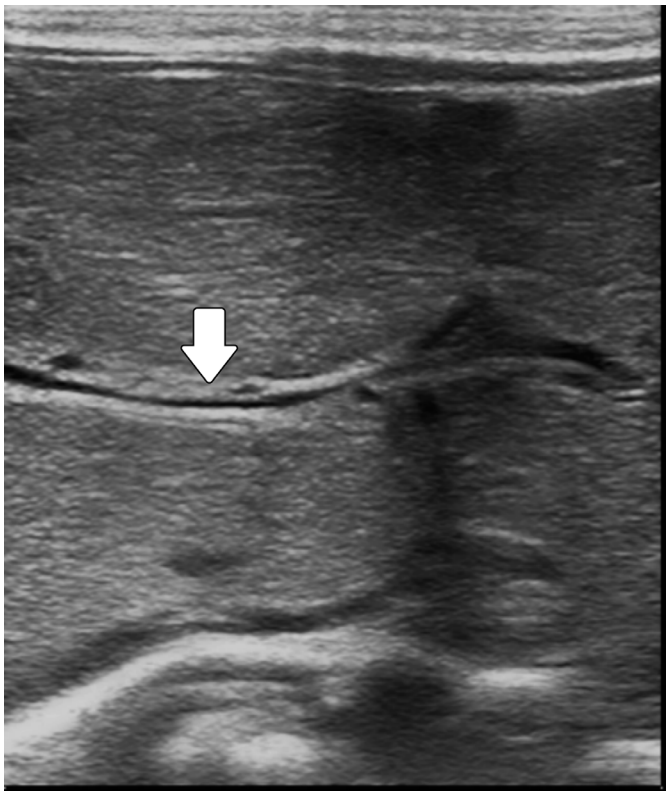

Figure 3 The transverse section of the left branch of the portal vein (following P-TN+vdHLAP C). P-TN+vdHLAP C, point-of-care ultrasound-guided tip navigation with visualised directional high-frequency linear array probe compression.

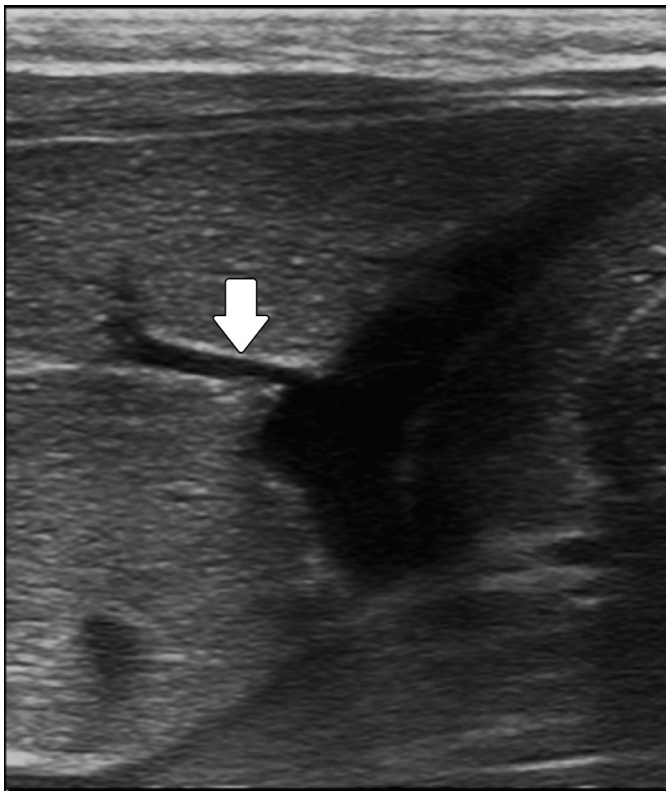

Figure 4 The ventral branch of the left inner segment of the portal vein (prior to P-TN+vdHLAP C). P-TN+vdHLAP C, point-of-care ultrasound-guided tip navigation with visualised directional high-frequency linear array probe compression.

(6) After the completion of the UVC procedures, the POCUS implementers will record the location of the umbilical catheter tip and complications among subjects with one-time UVC success, non-one-time UVC success and final UVC success. The data will be collected using a standardised and defined Access database.

Routine care

For critical neonates requiring immediate intravenous access, we have established a protocol to initiate peripheral intravenous access while the UVC placement is attempted. This ensures that emergency intravenous infusions can be administered promptly. In cases where UVC placement is delayed or complications are encountered, the critical neonates are closely monitored, and alternative central venous access methods are employed as needed.

To ensure strict adherence to aseptic standards across all participating centres, we implemented the following measures: Standardisation of operating procedures: Comprehensive standard operating procedures (SOPs) for aseptic handling were established for all participating centres. These SOPs encompassed the entire process, from environmental preparation, hand hygiene and use of sterile instruments to waste disposal. Standardised training: Prior to the commencement of the study, all researchers and operators at each centre underwent standardised training in aseptic operation techniques and successfully passed the required examinations. Detailed documentation: All aseptic procedures were meticulously documented, including procedural timing, operator identification, sterile instruments used, procedural details and any anomalies observed. These records serve as critical components of the study data for subsequent analysis and auditing. Regular audit and supervision: Each centre established a quality control team led by the head nurse, responsible for conducting regular audits of aseptic procedure implementation. Audit methods included on-site supervision, electronic surveillance review and record review. Cross-centre coordination and feedback: A multicentre coordination meeting was held quarterly via online Tencent meetings to share experiences and challenges encountered during the implementation of aseptic procedures, identify potential issues promptly and promote best practices across all centres.

With the exception of the different UVC interventions in the two groups, all feeding and treatment strategies are the same in both groups and will be performed according to the protocol of the NICUs.

Outcomes

The researchers will assess outcome measures at seven specific time points: the instant of catheter placement, 12 hours after placement, 24 hours after placement, 48 hours after placement, 7 days after placement, the instant of catheter removal and discharge. The assessment of

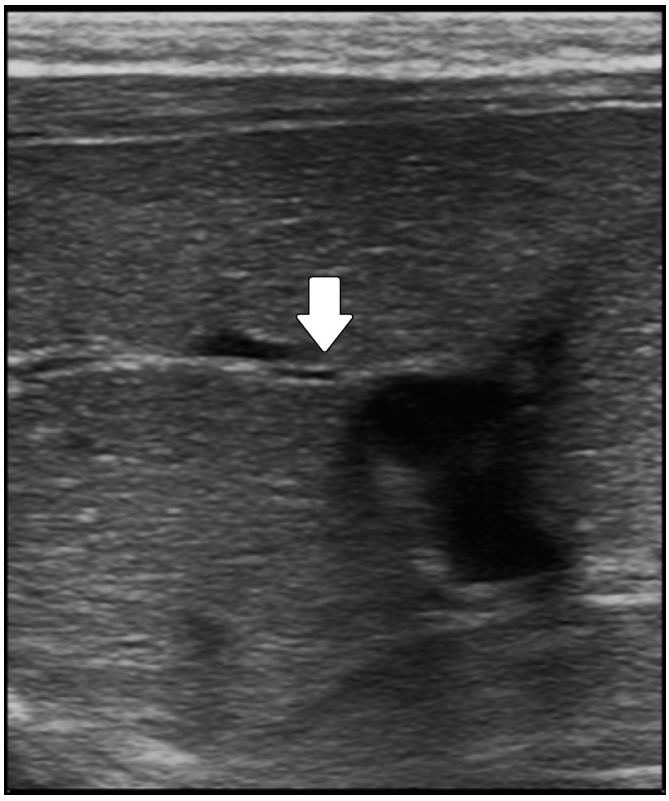

Figure 5 The ventral branch of the left inner segment of the portal vein (following P-TN+vdHLAP C). P-TN+vdHLAP C, point-of-care ultrasound-guided tip navigation with visualised directional high-frequency linear array probe compression.

outcome measures will be conducted by the POCUS implementers, and the corresponding data-collection intervals will be delineated in the participants' timelines (table 1).

The primary outcome is the success rate of UVC. Successful UVC is defined as confirmation using POCUS that the tip of the umbilical catheter is positioned at the entrance of the inferior vena cava into the right atrium.

One-time UVC success

The umbilical catheter is successfully inserted at the entrance of the inferior vena cava into the right atrium on the first attempt, without any external adjunctive operations during the procedure.

One-time UVC failure

The umbilical catheter is not successfully inserted at the entrance of the inferior vena cava into the right atrium on the first attempt, without any external adjunctive operations during the procedure.

Non-one-time UVC success

The umbilical catheter is successfully inserted at the entrance of the inferior vena cava into the right atrium following the implementation of the respective intervention measures in the intervention and control groups.

UVC failure

The umbilical catheter is not successfully inserted at the entrance of the inferior vena cava into the right atrium following the implementation of the respective intervention measures in the intervention and control groups.

Final UVC success

The umbilical catheter is successfully inserted at the entrance of the inferior vena cava into the right atrium following the implementation of the respective intervention measures in the intervention and control groups under the premise of failure and subsequently using the intervention method of the other group.

Final UVC failure

The umbilical catheter is not successfully inserted at the entrance of the inferior vena cava into the right atrium following the implementation of the respective intervention measures in the intervention and control groups under the premise of failure and subsequently using the intervention method of the other group.

The secondary outcomes are listed below.

Monitoring indicators during UVC: The time of UVC (ie, the total time from the insertion of the umbilical catheter into the umbilical vein opening to the confirmation of the tip of catheter successfully reaching the target position by POCUS), the total number of umbilical catheter insertions, the reason for one-time UVC failure, whether external adjunctive operations are needed during the procedure, the type of external adjunctive operations used and the actual depth of umbilical catheter placement.

Postoperative monitoring indicators for UVC: POCUS-guided indicators, including the location of the umbilical catheter tip; the incidence of complications, including thrombus, complications related to the liver (eg, portal venous gas embolism, liver abscess, hepatic haematoma, extravasation of fluid into the liver parenchyma and ascites), pleural effusion and pericardial effusion and other indicators, including the total number of days of umbilical catheter indwelling, reason for umbilical catheter removal and occurrence of catheter-related bloodstream infection.

Participants' timeline

The study involves a preoperative 10 min POCUS-based measurement of ultrasound parameters of vessels involved in the UVC pathway, an intraoperative evaluation of UVC and postoperative follow-up until discharge. Table 1 presents the time table of the activities planned during the study.

Sample-size calculation

PASS (V.2021) software was used to calculate the sample size for this study. The primary objective is to demonstrate the superiority of the P-TN+vdHLAP C technique in terms of UVC. The primary outcome measure is the success rate of UVC. Based on the preliminary experiments and relevant literature,[10] it is anticipated that the

Table 1 The time table of the activities planned during the study

Time points	Admission day	The instant of UVC placement	12 hours postplacement	24 hours postplacement	48 hours postplacement	7 days postplacement	The instant of catheter removal	Discharge
Enrolment	×							
Inclusion/exclusion criteria	×							
Informed consent	×							
Allocation	×							
Randomisation	×							
Interventions	×							
Intervention group	×							
Control group								
Assessment								
The success rate of UVC		×						
The time of UVC		×						
The total number of umbilical catheter insertions		×						
The incidence of complications			×	×	×	×		
Thrombus								
Related to the liver								
Pericardial effusion								
Catheter-related bloodstream infection								
The total number of days of catheter indwelling								

UVC, umbilical venous catheterisation.

intervention group would achieve a success rate of 95%, while the control group would achieve a success rate of 60%. A power of 90% (power=0.90) and an alpha level of 0.05 (α=0.05) were set, with a sample size ratio of 1:1 between the two groups. Accounting for a dropout rate of 20%, the required sample size for each group is determined to be a minimum of 24, resulting in a total required sample size of 48 across both groups.

$$N_3 = \frac{2\left[Z_{\alpha/2}\sqrt{2\bar{p}\bar{q}}+Z_{\beta}\sqrt{p_0q_0+p_1q_1}\right]^2}{(p_0-p_1)^2}$$

In the NICU of Fujian Children's Hospital, approximately 60 infants undergo UVC annually. Similar enrolment rates are observed at the other two participating hospitals. Given that 70% of these infants are expected to meet the eligibility criteria for this study, we estimate that it will be feasible to recruit a total of 100 participants within ten months.

Recruitment

The recruitment process of the trial is as follows: Infants admitted to the NICU within 72 hours of birth and requiring UVC are promptly assessed by our study staff. All eligible infants are then scheduled for recruitment. Once the legal guardian of the infant completes the admission procedures, our study staff escorts her/him to the subjects' reception room and provides comprehensive information about the study, including verbal explanations, information letters and participant consent forms. On obtaining written informed consent, the study staff contact the person in charge of randomisation to obtain the specific group allocation and inform the guardian about the treatment group they are allocated to: either the intervention group receiving P-TN+vdHLAP C or the control group receiving P-TL.

The principal investigator and the three other study staff members (neonatologists) participating in the trial actively work in the NICUs and have a schedule that guarantees the constant presence (24 hours/day) of the principal investigator or at least one of the study staff members responsible for recruiting participants, giving adequate information to guardians and following the ongoing study.

Allocation

In this study, we will generate random numbers using the 'random' package of R (V.4.3.2) and set a specific random seed (123) by using the 'set.seed()' function to maintain result reproducibility. To enhance the integrity of our research, we will implement a centralised randomisation system to ensure allocation concealment. A researcher from the university, henceforth referred to as the 'randomisation person,' is tasked with preparing the randomisation table and remains uninvolved in any other study procedures. The generated random numbers are sealed in opaque envelopes and kept by the randomisation person, who will open them after the participant is enrolled. On identification of an eligible participant, the study staff will contact the randomisation person to obtain the specific group allocation.

Blinding

This study employs a single-blind design. The physicians and head nurses in charge of the infants, the ultrasound physician, data collectors, as well as personnel responsible for statistical analyses will remain blinded to the intervention up to the conclusion of the study. Details regarding intervention allocation are securely enclosed within opaque envelopes in the custody of the randomisation person, and are stored in a secure administrative location.

Group assignments will be revealed 8 weeks after the completion of the intervention. In case of any adverse reactions during the trial, the physician must promptly report such incidents to ensure appropriate management by the principal investigator. Should unblinding be deemed necessary by the principal investigator following an adverse event occurrence or request for further medical action, only then would disclosure occur solely between the principal investigator and the physician without dissemination among the other research team members.

Statistical methods

Statistical analyses will be conducted by a seasoned statistician who will not have direct involvement in the study. We will use intention-to-treat analyses and carry out sensitivity analyses to address non-ignorable missing data.

The data will be entered twice using Epidata (V.3.1) and analysed using R (V.4.3.2) statistical software. Continuous data that follow a normal distribution will be presented as mean±SD, and compared between the intervention group and the control group by using a t-test. Non-normally distributed continuous data will be presented as median and IQR and will be compared between the groups by using the Mann-Whitney U test. Categorical data will be presented as frequency (percentage) and will be compared between the intervention group and the control group by using either the χ^2 test or the Fisher' exact probability test. A $p<0.05$ will be considered statistically significant.

Data collection, management and monitoring

Data collection will be carried out by two dedicated data collectors at our research centre, by using case report forms, which will then be inputted into an electronic data-capture system. Subsequently, another data collector will conduct a thorough review of the entered data to ensure accuracy. Once the data have been inputted, the database will be locked and inaccessible to any unauthorised personnel for reading or modification. Only the principal investigator holds complete access rights to read, modify and export the data. Following database locking, all modifications will be meticulously logged.

We will establish a data monitoring committee (DMC), which will be responsible for overseeing the quality of

the data. The DMC is an independent third party that is not affiliated with the researchers or sponsors and has no conflicts of interest with this study. It will conduct a review of the study data every 6 months to ensure its quality.

Harms and auditing

The ethics committee of Fujian Children's Hospital is responsible for ensuring the safety and quality control of this study. They are authorised to provide suggestions for modifying the study design to protect the subjects, with the final decision being made by the principal investigator. Prior to enrolment, all subjects' legal guardians must sign an informed consent form.

During the UVC placement process, there may be adverse events caused by difficulty in locating the tip of the umbilical catheter or operative trauma, such as arrhythmia, vascular injury and liver injury. To avoid complications, the procedure should be performed gently, and the ultrasound probe direction should be dynamically adjusted to ensure that the ultrasound beam is perpendicular to the umbilical catheter, achieving full visualisation of the catheter. When severe complications related to UVC are observed, immediate POCUS-guided assessment of the tip position and organs should be performed. After a definite diagnosis is made, the UVC should be immediately removed, and appropriate treatment should be given according to the condition of the infant.

When unforeseen circumstances arise, the physician is required to promptly notify the principal investigator within 24 hours of occurrence. The principal investigator is then responsible for reporting the event to the ethics committee of Fujian Children's Hospital for documentation purposes. In cases where necessary, appropriate procedures must be followed to lift any blinding to ensure the safety of the trial participants.

A coordinator is appointed by the ethics committee of Fujian Children's Hospital to conduct online inspections of the research centres every 3 months, and ensure that there is at least one on-site visit to all research centres annually. During each visit, the coordinator must verify the research protocol, ethics approval, case report form, informed consent form, etc. With regard to the case report form, it is essential to confirm that all fields, including names, ID numbers, random numbers, gender, assigned intervention schemes, adverse events and outcome indicators, for each patient are completed in full.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

ETHICS AND DISSEMINATION

This research protocol has been approved by the ethics committee of Fujian Children's Hospital (protocol number 2024ETKLRK09019) and has been registered on the Chinese Clinical Trial Registry (ChiCTR2400090737). The research protocol, informed consent forms, procedures for obtaining informed consent and confidentiality measures for individual data have all been approved by the ethics committee. Any modifications to the study protocol that may affect its implementation will be submitted to the ethics committee for review. Prior to enrolment, written informed consent will be obtained from the legal guardians of all participants by the study staff. The research results will be submitted to peer-reviewed journals, and abstracts will be submitted to relevant national and international conferences. The final trial dataset will be made available to the corresponding author on removal of participant identities. The authors of the published paper should accurately represent the academic contributions of individuals who designed and implemented the trial, analysed the data and wrote the paper.

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