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Study protocol

A Multicenter Double-blind Randomised Parallel Group Phase Three Superiority Clinical Trial on the Effectiveness of Dextran 40 Compared to Normal Saline in Preventing Dengue Shock in the Early Leakage Phase of Dengue Haemorrhagic Fever: Study Protocol

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Abstract

Background: Dengue haemorrhagic fever (DHF) remains a major cause of morbidity in tropical countries, with progression to shock contributing substantially to mortality. Early plasma leakage with organ hypoperfusion may represent a critical therapeutic window for intervention. This study evaluates whether dextran-40 is superior to normal saline in preventing dengue shock during the early leakage phase of DHF.

Methods: The Dextran in the Early Leakage Phase of Dengue Prevents Shock (DELPODS) study is a multicenter, double-blind, randomised, parallel-group phase III superiority trial conducted in Sri Lanka. Adults aged ≥18 years with confirmed dengue fever and evidence of early plasma leakage with organ hypoperfusion are randomised to receive either intravenous dextran-40 (5 mL/kg; maximum 250 mL) or 0.9% normal saline at an equivalent dose infused over 2 hours. Patients with advanced plasma leakage, established shock, pregnancy, acute kidney injury, advanced chronic kidney disease, severe heart failure, severe liver disease, or dextran hypersensitivity are excluded. The planned sample size is 218 participants.

Outcomes: The primary outcome is the incidence of shock within 48 hours of randomisation. Secondary outcomes include maintenance of haemodynamic stability, time to haemodynamic instability, need for additional fluid therapy, clinical outcomes at discharge, and safety outcomes including fluid overload, acute kidney injury, and hypersensitivity reactions.

Ethics and Registration: Ethical approval was obtained from the Ethics Review Committee of the Faculty of Medical & Allied Sciences, Rajarata University of Sri Lanka (22 June 2022). The trial is registered with the Sri Lanka Clinical Trial Registry (SLCTR/2022/003; U1111-1272-4389).

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1a. Title stating the trial design, population, and interventions

A multicenter double-blind randomised parallel group phase III superiority clinical trial on the effectiveness of dextran-40 compared to normal saline in preventing dengue shock in the early leakage phase of dengue haemorrhagic fever.

1b. Structured summary of trial design

Table 1: WHO Trial Registration Data Set items. Adapted from Sri Lankan Clinical Trial Registry

Primary registry and trial identifying number	Sri Lanka Clinical Trial Registry SLCTR/2022/003
Date of registration in the primary registry	07 Feb 2022
Secondary identifying number	Not applicable
Universal trial number	U1111-1272-4389
Sources of monetary or material support	None
Primary sponsor	Unsponsored
Secondary sponsor	NA
Contact for public queries	Dr Ruwanthi Bandara. +94777801677 +94812389106 ruwanthibandara@yahoo.com
Contact for scientific queries	Dr. Chamara Sarathchandra +94774743366 +94252227706 nilupulchamara@gmail.com
Public title	Dextran versus normal saline in preventing dengue shock during the early leakage phase of dengue haemorrhagic fever: the DELPODS study
Scientific title	A multicenter double-blind randomised parallel group phase III superiority clinical trial on the effectiveness of dextran-40 compared to normal saline in preventing dengue shock in the early leakage phase of dengue haemorrhagic fever. **D**extran in the **E**arly **L**eakage **P**hase **o**f **D**engue Prevents **S**hock (**DELPODS**) study
Countries of recruitment	Sri Lanka
Health condition	Dengue haemorrhagic fever
Interventions	Arm 1 Participants in this arm will be randomly assigned to receive dextran-40 (5 mL/kg, maximum 250 mL) infused intravenously over 2 hours, administered at the onset of organ hypoperfusion during the early leakage phase. Arm 2 Participants in this arm will be randomly assigned to receive 0.9% normal saline (5 mL/kg, maximum 250 mL) infused intravenously over two hours, administered at the onset of organ hypoperfusion during the early leakage phase.
Key inclusion and exclusion criteria	Inclusion criteria 1. Aged 18 and above 2. Having confirmed dengue fever. Exclusion criteria 1. Patients who have evidence of advanced plasma leakage or established shock on admission 2. Known hypersensitivity to dextran 3. Pregnant mothers 4. Patients with acute kidney injury 5. Advanced CKD (stage V) 6. Severe heart failure (NYHA class III & IV)

	7. Severe liver disease (Child's C)
Study type	Purpose : Treatment Allocation : Randomised controlled trial Masking : Blinded (masking used) Assignment : Parallel Type of endpoint: Efficacy Phase 3
Date of first enrollment	2022-10-07
Sample size	218
Recruitment status	Currently recruiting
Primary outcomes	Incidence of shock within 48 hours of randomisation
Key secondary outcomes	1. Maintenance of haemodynamic stability at 1 hour, 6 hours, 12 hours, 24 hours, and 48 hours after intervention and time to first haemodynamic instability after intervention. 2. Need for additional fluid therapy 3. Clinical outcomes at hospital discharge 4. Safety outcomes – Incidence of fluid overload, acute kidney injury, and hypersensitivity reactions to dextran.
Ethics review	Status: Approved Approval date: 22nd June 2022 Contact: Ethics Review Committee, Faculty of Medical & Allied Sciences, Rajarata University of Sri Lanka.
Data sharing statement	All individual participant data (IPD) collected during the trial will be deidentified before sharing. The deidentified IPD, statistical code, and data dictionary will be made available for researchers whose purposes have been approved by an independent review committee identified for this purpose. The data may be used to achieve the objectives discussed and for meta-analysis. For any further use or to obtain the data, please email nilupulchamara@gmail.com. Data will be available for use immediately after publication and for at least 10 years.

2. Protocol version date and identifier: Version 7

3a. Names, affiliations and roles of protocol contributors

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3b. Name and contact information of the trial sponsor

This is an investigator-sponsored clinical trial.

3c Role of the trial sponsor and funders in trial design

As this is an investigator-initiated, unsponsored trial, the investigators assume full responsibility for the study design, conduct, data collection, analysis, interpretation, and publication of results. No external entity has influenced any aspect of the trial.

3d. Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial

Coordinating Site

Composition:

The coordinating site is the University Medical Unit at the Teaching Hospital Anuradhapura, affiliated with Rajarata University of Sri Lanka. It will serve as the central hub for trial coordination, supported by the University Medical Unit at the Teaching Hospital, Peradeniya.

Roles and Responsibilities:

The coordinating site will lead the overall conduct of the trial, ensuring compliance with Good Clinical Practice and all ethical requirements. It will coordinate investigator and study staff training, manage trial documentation, and maintain effective communication among participating sites. The coordinating team will ensure that adverse events and safety signals are reported promptly to the steering committee and will oversee all logistical aspects of the study to ensure smooth and efficient trial operations.

Steering Committee

Composition:

Co-principal investigators (CS & RB) and two academic leads (SS & IBG) from each study centre.

Roles and Responsibilities:

The Steering Committee provides strategic oversight and scientific leadership for the trial. It is responsible for approving the trial protocol and any amendments, and for monitoring recruitment progress, protocol adherence, and participant safety. The committee reviews reports from the data management team and the safety monitoring committee, making informed decisions regarding the continuation, modification, or early termination of the trial in consultation with regulatory authorities and ethics committees.

Endpoint Adjudication Committee (EAC)

Composition:

Independent clinicians with expertise in infectious diseases, critical care, cardiology, and nephrology, not directly involved in patient recruitment or care at the study sites.

Roles and Responsibilities:

The Endpoint Adjudication Committee (EAC) independently reviews and adjudicates all primary and secondary clinical endpoints, including shock incidence, haemodynamic stability, fluid overload, and acute kidney injury. Endpoints are evaluated using anonymised clinical data, laboratory results, and imaging reports, with assessors blinded to treatment allocation. The committee ensures consistency, objectivity, and reliability in endpoint classification across study sites and provides adjudication reports to the steering committee and statisticians for final analysis.

Data Management Team

Composition:

A dedicated team of data managers and a statistician based at the coordinating site.

Roles and Responsibilities:

The Data Management Team is responsible for developing and maintaining the trial database, ensuring secure data collection, entry, and storage, and conducting regular quality checks and validation. The team implements real-time monitoring systems to identify missing data, inconsistencies, and protocol deviations. It provides regular recruitment and data quality reports to the coordinating site and the steering committee. It also supports the statistician in preparing interim and final datasets for analysis.

Data and Safety Monitoring Board (DSMB)

Composition:

Independent experts in clinical trials, infectious diseases, biostatistics, and ethics.

Roles:

The Data and Safety Monitoring Board (DSMB) periodically reviews unblinded safety and efficacy data to ensure participant well-being and trial integrity. Based on its assessments, the DSMB provides independent recommendations on whether the trial should continue, be modified, or be terminated on safety grounds.

Trial Secretariat

Composition:

Research assistants, coordinators, and administrative staff at the coordinating site.

Roles:

The trial secretariat manages the day-to-day operations of the study, including scheduling, communication, and document management. It provides administrative and logistical support to site teams and serves as the first point of contact for operational queries, ensuring smooth coordination and efficient trial conduct.

4. Trial registration

Name of trial registry, identifying number (with URL), and date of registration

This trial was registered in the Sri Lanka Clinical Trial Registry on 7th February 2022.

https://slctr.lk/trials/slctr-2022-003.

5. Protocol and statistical analysis plan

Where the trial protocol and statistical analysis plan can be accessed

It will be available at the ERC of the Faculty of Medicine, Rajarata University

6. Data sharing

Where and how the individual deidentified participant data (including data dictionary), statistical code, and any other materials will be accessible

Deidentified individual participant data (IPD), the data dictionary, and statistical analysis code will be made available upon reasonable request to the corresponding author. Requests will be reviewed by an independent data access committee to ensure scientific merit and ethical compliance. Approved data will be shared through secure institutional data-sharing platforms after publication and will remain available for at least 10 years.

7. Funding and conflict of interest

7a. Sources of funding and other support (eg, supply of drugs)

This study is conducted without external funding. All study-related activities, including personnel time and consumables, are supported by institutional resources of the participating university medical units. No pharmaceutical or commercial entity has provided financial or material support.

7b. Financial and other conflicts of interest for principal investigators and steering committee members

No competing interest for principal investigators, steering committee members or any other investigator.

8. Dissemination policy

Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, reporting in trial registry, plain language summary, publication)

We have registered the trial in the Sri Lanka Clinical Trials Registry. Within one year of completing the trial, we will report the results to the registry. Study results will not be individually communicated to participants due to the acute nature of the illness and the anonymised analysis of outcomes. Results will be disseminated through peer-reviewed publications and academic presentations.

INTRODUCTION

9 Background and rationale

9a. Scientific background and rationale, including a summary of relevant studies

Dengue infection is a major cause of acute febrile illnesses in tropical and subtropical regions and is associated with substantial morbidity and mortality. While most infections are self-limiting, a proportion of patients develop dengue haemorrhagic fever (DHF), characterised by increased vascular permeability, plasma leakage, and risk of progression to shock [1]. The critical phase typically begins around defervescence [1] and represents a short but clinically important period during which early intervention may prevent deterioration.

The mechanisms responsible for plasma leakage in DHF are not yet fully understood. Structural destruction of the vascular endothelium is not a prominent feature, as suggested by the rapid reversibility of plasma leakage and the absence of persistent inflammatory damage [1]. This has led to the view that plasma leakage in DHF reflects a transient functional disturbance of endothelial barrier regulation rather than irreversible endothelial injury. Evidence from clinical and experimental studies indicates that disruption of the endothelial glycocalyx occurs in conditions associated with capillary leak, including severe dengue. Circulating markers of glycocalyx degradation have been associated with disease severity, supporting a contributory role for endothelial surface layer dysfunction in the development of plasma leakage [2, 3].

Management of DHF during the critical phase is largely supportive and centres on judicious intravenous fluid therapy to maintain effective circulating volume while minimising the risk of fluid overload. Crystalloid solutions are recommended as first-line therapy, with colloids reserved for selected clinical situations [1,4]. Dextran-40 is a colloid solution with a long history of use in dengue management as a plasma volume expander due to its intravascular retention and oncotic properties.In addition to its volume-expanding effects, dextran-40 possesses biological properties that may influence endothelial function. Experimental data from other disease models suggest that dextran compounds can interact with endothelial surfaces and modulate pathways involved in regulating the endothelial barrier [5-7]. Evidence on dextran's endothelial effects in humans comes from a dextran fractional clearance study conducted in Vietnam. Serial clearance measurements in 15 severe dengue patients and 16 healthy controls showed no significant differences in dextran clearance at any time point. The normal clearance profiles observed despite vascular leakage may reflect a transient improvement in endothelial permeability due to physical and/or electrostatic interactions between dextran and the endothelial surface glycocalyx [8]. These observations raise the possibility that early administration of dextran-40 during the critical phase of DHF may offer benefits beyond transient intravascular volume expansion. Concerns regarding adverse effects, including hypersensitivity reactions, renal impairment,

thrombocytopenia, and interference with blood cross-matching, have limited the routine use of dextran-40. However, available evidence suggests that such complications are uncommon at lower doses and can be mitigated through appropriate patient selection and close monitoring [9-11].

Accordingly, this study is designed to evaluate whether administration of a low-dose dextran-40 infusion at the early phase of the critical phase reduces progression to shock and improves haemodynamic stability compared with standard crystalloid therapy. The scientific hypothesis underpinning this trial was previously proposed by the investigators and published as a hypothesis article [12]. The present study is designed to empirically test that hypothesis using.

9b. Explanation for the choice of the comparator

Normal saline was selected as the comparator in this trial because it represents the standard of care for fluid resuscitation in patients with dengue haemorrhagic fever (DHF) during the early critical phase. Current practice guidelines recommend normal saline as the first-line therapy for managing plasma leakage and preventing shock, given its wide availability, low cost, and established safety profile. Using normal saline as the comparator allows the trial to directly assess whether dextran 40, a colloid with potential benefits in sustaining intravascular volume and haemodynamic stability, provides superior clinical outcomes compared with standard management. This choice ensures clinical relevance, enhances the generalisability of findings to real-world practice, and enables a fair evaluation of dextran against the most widely used and accepted treatment option.

STUDY HYPOTHESIS

Null hypothesis (H0): Dextran infusion in early DHF does not prevent shock or improve haemodynamic status.

Alternative Hypothesis (H1): Dextran infusion in early DHF prevents shock and improves haemodynamic status.

10. OBJECTIVES

General objective

The primary objective of this study is to evaluate whether dextran administration is superior to normal saline during the early critical phase of dengue haemorrhagic fever in preventing shock, prolonging haemodynamic stability for a longer period than normal saline does, and improving overall clinical outcomes.

Specific objectives

1. To assess the superiority of dextran administration in the early critical phase in preventing shock over normal saline in DHF.

2. To assess the superiority of dextran administration in the early critical phase in achieving haemodynamic stability over normal saline in DHF 1 hour after the intervention.

3. To ascertain whether administering dextran during the early critical phase is more effective than using normal saline in maintaining haemodynamic stability in DHF patients.

4. To compare the clinical outcomes and treatment-related adverse effects on discharge from the hospital and the duration of hospital stay.

METHODS: PATIENT AND PUBLIC INVOLVEMENT, TRIAL DESIGN

11. Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research. This trial evaluates two standard intravenous fluids routinely used in the acute management of dengue haemorrhagic fever, with interventions determined by time-critical clinical criteria. Given the acute nature of the illness and the need for rapid treatment decisions, patient and public involvement at the design stage was not feasible. The study outcomes were selected based on clinical relevance and existing dengue management guidelines.

12. Trial design

The DELPODS study is a multicenter, double-blind, randomised, phase III superiority clinical trial with a parallel-group design and a 1:1 allocation ratio.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

13. Trial setting

This study is currently being conducted at the university medical units of Teaching Hospital Anuradhapura, Sri Lanka and Teaching Hospital Peradeniya, Sri Lanka. Teaching Hospital Anuradhapura, affiliated to Rajarata University of Sri Lanka, is the only tertiary care hospital in the Anuradhapura district with a population of 959,372. The Teaching Hospital Peradeniya, a tertiary care hospital affiliated to the University of Peradeniya, is located in the Kandy district with a population of 1,461,130. Both units provide tertiary care and have a 24/7 non-discriminating medical admission policy. Eligible patients who get admitted to the above units are being recruited for the study.

14. Eligibility criteria

All patients aged 18 and above who present to the above units with dengue fever (as confirmed by a positive NS-1 antigen, PCR, or dengue IgM) are assessed for eligibility. Participants with ultrasound evidence of plasma leakage are recruited for the study.

Exclusion criteria include evidence of advanced plasma leakage or shock, hypersensitivity to dextran, pregnant mothers, acute kidney injury, advanced chronic kidney disease (stage IV & V), advanced heart failure (NYHA III &IV), and advanced liver disease (Child's C).

15. Intervention and comparator

15a. Intervention and comparator with sufficient details to allow replication.

The intervention of this study is dextran-40. Currently, it is recommended to be used as a plasma expander in dengue shock in addition to the crystalloid, 0.9% normal saline [1, 4]. Comparator is the crystalloid, normal saline, which is recommended by current practice guidelines as the standard fluid therapy during the leakage phase [1,4]. When participants show evidence of organ hypoperfusion, defined as reduced urine output (<0.5 mL/kg/hour) for two consecutive hours, they will be randomised to receive either dextran or normal saline. A total of 5 mL/kg (maximum 250 mL) of dextran or normal saline is infused over the next two hours. Following that, while closely monitoring, standard fluid treatment is started according to the Sri Lankan national guidelines. If the urine output drops again, the same treatment given earlier will be infused at the same rate over two hours. Infusing the study drug will be limited to two doses. A ward nurse will set the infusion under the supervision of a research assistant.

Commercially available dextran-40 is dissolved in normal saline; therefore, both treatment groups will receive an equal volume of normal saline as part of the study. The only difference between the two groups is that the intervention group receives 25 g of Dextran 40 in addition to normal saline per dose.

15b. Criteria for discontinuing or modifying interventions

Criteria for discontinuing a trial participant include the development of shock at any stage during the trial procedure, the development of serious drug side effects (anaphylaxis, acute kidney injury, and fluid overload), the necessity to transfuse other colloids, blood, or blood products, and participant request.

15c. Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (eg, drug tablet return, sessions attended)

To improve adherence to the intervention and comparator protocols, several strategies have been implemented. All study procedures have been standardised through detailed written protocols and training sessions for the medical and nursing staff who administer the interventions. A research assistant directly supervises each infusion to ensure correct dosing and timing of administration according to the randomisation arm. Adherence has been optimised through standardised infusion algorithms and infusion-pump presets specifying rate, volume, and timing for the assigned fluid (dextran 40 or normal saline) during the early leakage phase.

Ward nurses receive training on the study protocol and documentation requirements, while adherence checklists are maintained for each participant to track infusion volumes, duration, and monitoring parameters. Regular team meetings and feedback sessions are held to reinforce adherence, and any protocol deviations will be documented and reviewed to ensure quality control throughout the trial.

15d. Concomitant care permitted or prohibited during the trial.

Infusion of other colloids, blood and blood products is prohibited after recruitment to the trial. If these products are essential for managing a particular participant, they will be removed from the study. Symptomatic treatment for fever with paracetamol, vomiting with antiemetics, and oral and intravenous normal saline will be permitted.

16. Outcomes

Primary outcome

Incidence of shock within 48 hours of randomisation

Secondary outcomes

1. Maintenance of haemodynamic stability at 1 hour, 6 hours, 12 hours, 24 hours, and 48 hours after intervention and time to first haemodynamic instability after intervention.
2. Need for additional fluid therapy
    - •Total intravenous fluid volume administered during the critical phase (first 48 hours).
    - •Requirement for fluid boluses to maintain haemodynamic stability at 12 hours, 24 hours, 36 hours and 48 hours after intervention.
3. Clinical outcomes at hospital discharge
    - •Duration of hospital stay.
    - •Proportion requiring intensive care unit admission.
    - •Mortality.

4. Safety outcomes – Incidence of fluid overload, acute kidney injury (defined by KDIGO criteria), and hypersensitivity reactions to dextran.

Definitions

Compensated shock

Normal systolic pressure, tachycardia with narrow pulse pressure (< 30 mmHg)

Decompensated shock

Systolic blood pressure less than 90 mmHg and /or mean arterial pressure less than 65 mmHg.

Haemodynamic stability

Normal blood pressure with pulse pressure more than 30 mmHg, absence of tachycardia and urine output of 0.5mL/kg/hour or more OR requirement of rescue colloid therapy (beyond study protocol) for haemodynamic instability.

Fluid overload

Fluid overload can be categorised based on severity. Mild fluid overload is characterised by the presence of fine basal lung crackles or periorbital oedema without any dyspnea. Moderate fluid overload includes these signs along with dyspnea. Severe fluid overload is manifested as pulmonary oedema.

17. Harms

17.1 Definitions

Harms will be defined and assessed in accordance with ICH-GCP guidelines:

Adverse Event (AE): Any untoward medical occurrence in a participant administered a study intervention, not necessarily causally related.

Serious Adverse Event (SAE): An event that results in death, is life-threatening, requires or prolongs hospitalisation, results in persistent or significant disability, or is otherwise medically significant.

Adverse Reaction (AR): An AE judged by the investigator to be causally related to dextran 40.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An SAE that is both unexpected (not consistent with known safety profile) and suspected to be related to dextran 40.

17.2 Prespecified Harms

Based on the known safety profile of dextran-40, the following harms will be specifically monitored:

Fluid overload

Fluid overload is defined clinically as mild, moderate, or severe. Mild fluid overload presents with fine basal lung crackles or periorbital oedema without dyspnea, moderate fluid overload includes these signs along with dyspnea, and severe fluid overload is characterised by pulmonary edema. Monitoring involves daily clinical examination, assessment of oxygen saturation, and chest imaging when indicated.

Acute kidney injury (AKI)

Acute kidney injury (AKI) will be defined according to the KDIGO criteria as a rise in serum creatinine of ≥ 0.3 mg/dL within 48 hours, or a urine output of less than 0.5 mL/kg/hour for six hours or more. Monitoring for AKI will include baseline serum creatinine measurement, daily renal function tests, and continuous urine output monitoring to enable early detection and management.

Hypersensitivity reactions and anaphylaxis

Hypersensitivity reactions, including anaphylaxis, are defined according to WAO criteria. Monitoring should be conducted during and immediately after each infusion, with careful clinical observation for signs such as rash, urticaria, bronchospasm, or hypotension.

Haematological effects

The haematological effects of dextran may include thrombocytopenia or anaemia, particularly with repeated infusions; monitoring should be performed through daily complete blood counts. Furthermore, dextran can cause rouleaux formation or cross-match incompatibility during transfusion requests, interfering with blood cross-matching procedures.

Other SAEs

Any clinically significant unexpected adverse effect.

17.3 Assessment of Harms

Assessment of harms will be conducted through continuous monitoring during infusions, daily evaluations until hospital discharge, and a follow-up visit or telephone call 7-14 days after discharge to identify any delayed adverse effects. The severity of all harms will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0), where applicable. Each AE will be assessed by the investigator for causality and classified as not related, unlikely, possible, probable, or definite. The action taken in response to each harm, whether no change, dose withheld, intervention stopped, or additional treatment required, will be clearly documented.

17.4 Reporting of Harms

All AEs and SAEs will be documented in the Case Report Forms (CRFs). SAEs will be promptly reported to the principal investigator and the ethics review committee within 24 hours of identification. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the national regulatory authority and the ethics committee in accordance with International Council for Harmonisation – Good Clinical Practice (ICH-GCP) timelines to ensure regulatory compliance and participant safety.

17.5 Oversight and Stopping Rules

A Data Safety Monitoring Board (DSMB) will review safety data at regular intervals to ensure participant safety and trial integrity. The trial includes predefined stopping rules, such as detecting an excess of anaphylaxis, severe fluid overload, or acute kidney injury (AKI) in the dextran arm compared with the saline arm. In addition, any unexpected pattern of serious adverse events (SAEs) that the DSMB considers to pose an undue risk to participants will prompt recommendations for modification or early termination of the trial.

18. Participant timeline (Figure 1 & Figure 2)

All patients aged 18 and above who present to the above units with dengue fever (as confirmed by a positive NS-1 antigen, PCR, or dengue IgM) are assessed for eligibility. Those with evidence of third space fluid accumulation on ultrasound will be recruited for the study.

Participants will be closely monitored once recruited. During the run-in period, participants received standard fluid therapy. However, when a patient shows evidence of organ hypoperfusion, defined as reduced urine output (< 0.5 mL/kg/hour) for two consecutive hours, they will be randomised to receive either dextran or a crystalloid solution (normal saline). A total of 5 mL/kg (maximum 250 mL) of dextran or normal saline is infused over the next 2 hours. Following that, while closely monitoring, standard fluid treatment is started with normal saline and oral fluids. If the urine output drops again, an equal amount of the same drug will be infused over two hours. Infusion of the study drug will be limited to 2 doses. If a participant develops compensated or uncompensated shock at any stage of the study, the trial will be terminated, and care will be transferred to the treating clinicians. Participants will be closely observed during and after the study drug administration for drug side effects and the development of shock.

	Trial period			
	Enrolement		Post-randomisation	Close-out
Time point	**Admission**	**Onset of leakage**	**Critical phase**	**Discharge**
Enrolement				
Eligibility screen	X			
Informed consent	X			
Recruitement		X		
Randomisation			X	
Intervention or comparator				
Intervention group (Dextran infusion)			→	
Comparator group (normal saline infusion)			→	
Assessments				
Clinical review		X	X	X

Figure 1: Participant schedule for enrollment, interventions and assessments.

Adults (≥18 years) admitted with laboratory-confirmed dengue infection were screened for eligibility. Participants with ultrasound evidence of plasma leakage during the early critical phase were enrolled. Randomisation was performed when urine output fell below 0.5 mL/kg/hour for two consecutive hours. Participants were allocated in a 1:1 ratio to receive either dextran 40 (5 mL/kg; maximum 250 mL) or 0.9% normal saline (5 mL/kg; maximum 250 mL), administered intravenously over two hours.

Participants were closely monitored and received standard guideline-based care. If urine output again fell below 0.5 mL/kg/hour for two consecutive hours, a second dose of the allocated study fluid was administered (maximum two doses). Trial procedures were discontinued, and care transferred to the treating clinical team if shock or serious adverse events occurred. All randomised participants were included in the intention-to-treat analysis.

19. Sample size

Sample size was calculated using the formula for clinical trials by Rosner and the continuity correction by Fleiss [13, 14]. Among the outcomes of this trial, the primary outcome of interest is the development of dengue shock. Therefore, the sample size is calculated based on the expected difference at the time of shock entry. In a 2021 study, 23% of patients with dengue infection go into shock when managed according to current practice guidelines [15]. Investigators expect an absolute reduction of shock by 15% with the new testing drug. (Relative Reduction of 65.2%) Sample size was calculated to detect the above difference, at 80% power, 95% confidence interval with an enrolment ratio of 1:1. Calculated sample size for each arm is 91. After performing a continuity correction according to Fleiss [14], the sample size per arm is 103. After adding a 5% dropout rate, the sample size per arm is 109, and the total sample size across both groups is 218. All eligible participants admitted to the above units will be recruited to participate in the study after providing their consent.

20. Recruitment

Strategies for achieving adequate participant enrolment to reach the target sample size

Participants will be recruited through continuous, round-the-clock enrollment supported by staggered research assistant shifts and on-call investigators to capture all eligible cases. To minimise screen failures, we have defined enrollment criteria that are both stringent and pragmatic. Early admission of patients with suspected dengue from the emergency department will be encouraged, with rapid laboratory confirmation available 24/7 to avoid missing the enrollment window. The consenting process has been designed to be clear and straightforward, reducing delays. In addition, satellite hospitals in the region will be encouraged to refer eligible patients promptly to enrolling centres early in the course of illness. A participant-friendly environment will be maintained, ensuring that concerns are promptly addressed to minimise dropout rates.

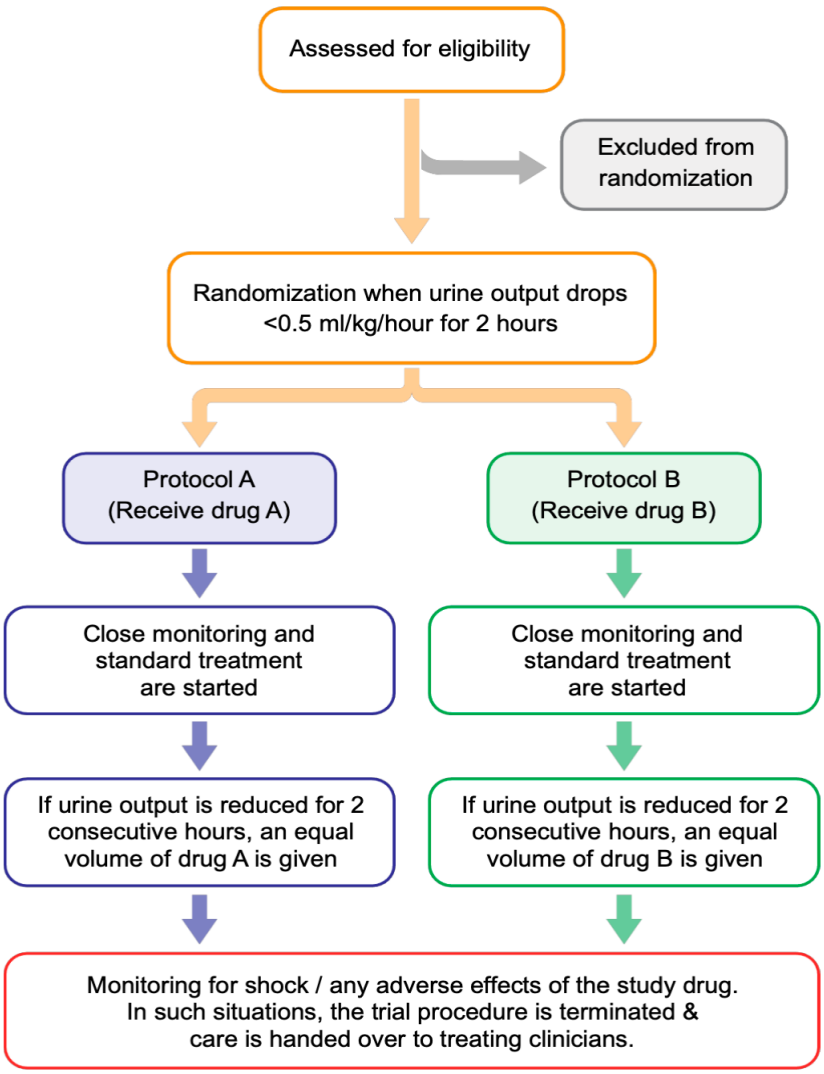

Figure 2: CONSORT flow diagram of the DELPODS trial

METHODS: ASSIGNMENT OF INTERVENTIONS

RANDOMISATION

21. Sequence generation

21a. Who will generate the random allocation sequence, and the method used

A computer-generated random allocation sequence was created in a 1:1 ratio by one of the co-principal investigators (CS) before the enrollment of the first participant using an online computer application [16].

21b. Type of randomisation (simple or restricted) and details of any factors for stratification. To reduce the predictability of a random sequence, other details of any planned restriction

Permuted block randomisation was done using an online computer application [16]. Varying block sizes were used, and block sizes are blinded to investigators to avoid predictability.

22. Allocation concealment mechanism

The random allocation sequence will be implemented using sequentially numbered, opaque, sealed envelopes prepared by an independent investigator not involved in participant enrolment or clinical management. Envelopes will be opened only after a participant meets randomisation criteria.

23. Implementation

The random sequence for trial group allocation in blocks was generated by one of the co-principal investigators (CS) using an online tool [16]. To prevent biased patient selection, the co-principal investigators from each unit, with the help of research assistants, will remotely screen new patient admissions and alert the medical staff to possible candidates. The patient's attending physicians are responsible for applying the protocol, determining patient eligibility, and verifying compliance with inclusion and exclusion criteria. However, informed consent will be taken by a research assistant outside the study group. Once the randomisation criteria are met, a research assistant opens the sealed envelope containing the allocation code and informs the attending clinicians. Other trial staff members have no access to the random allocation sequence.

24. Blinding

24a. Who will be blinded after assignment to interventions

Trial participants, investigators, care providers, outcome assessors, and data analysts will be blinded to treatment allocation. Only one research assistant from each centre will be aware of the coding system and will not disclose this information until after the trial is completed.

24b. How blinding will be achieved, and a description of the similarity of interventions

Normal saline and dextran containers (plastic bottles) with a similar external appearance are selected for the study. They will be covered with a paper bag to make the labels invisible. Two types of bottles will be named A and B by a research assistant who is not part of the research investigators. Therefore, the type of study drug is blinded to investigators, outcome assessors, treating physicians, participants, and the nurse setting the infusion. The radiologists performing the critical phase scanning will also be blinded to the day of the illness, signs and symptoms and investigation results.

24c. Circumstances under which unblinding is permissible

Unblinding will occur only upon request by the treating clinicians when necessary for the clinical management of patients. Our study will define two unblinding situations: a serious adverse event or the development of shock if requested by treating clinicians. In such situations, treating clinicians should inform the principal investigator, who will advise the research assistant to disclose the information to treating doctors. However, investigators will remain blinded during coding.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

25. Data collection methods

25a. Plans for assessment and collection of trial data

All data will be collected by a research assistant who is a medical or nursing graduate, and recorded in a CRF. Basic data regarding clinical features, comorbid medical conditions and their treatment will be collected by interviewing participants and reviewing previous medical notes. Results of investigations, ultrasound reports, fluid management charts and monitoring charts will be extracted from medical notes. All data will then be entered into a Microsoft Excel worksheet.

The attending doctors will assess outcomes. All data collection forms are available from the corresponding author on request

25b. Plans to promote participant retention and complete follow-up, including a list of any outcome

data to be collected for participants who discontinue or deviate from intervention protocols

We ensure a patient-centred approach is applied to all trial activities and interactions with trial participants. The study staff at each site will be available to participants to answer questions and address any concerns. As the trial concludes with discharge, there are no additional hospital visits. For participants who withdraw from the trial, no further information will be collected from the date of withdrawal.

26. Data management

Plans for data entry, coding, security, and storage, including any related processes to promote data quality. Reference to where details of data management procedures can be accessed, if not in the protocol

Study data will be initially recorded on paper case report forms (CRFs). Completed CRFs will undergo review for completeness and consistency before being submitted to the data management team. To ensure accuracy, a double data entry process will be employed, with two independent data entry staff members entering the same data into the database. Any discrepancies identified between the two entries will be reconciled against the original CRF. Range checks and programmed edit checks will be implemented within the database to identify implausible or missing values, which will then be queried and resolved in collaboration with the site. This process ensures that data captured on paper is transcribed accurately and reliably into the electronic database

All study data will be handled in accordance with good clinical practice and applicable data protection regulations. Access to study records and databases will be restricted to authorised personnel only, based on role-specific permissions. Both paper and electronic records will be stored in secure, access-controlled environments, with paper files kept in locked cabinets and electronic data maintained on validated, password-protected systems. Audit trails will capture all data entry, modifications, and deletions, including user identification, date, and reason for change. Data transfers will be encrypted, and regular backups will be performed to ensure continuity and disaster recovery. Any identifiable participant information will be coded or anonymised to protect confidentiality

Adverse events and medical history will be coded with the **Medical Dictionary for Regulatory Activities (MedDRA).** In contrast, concomitant medications will be coded using the **WHO Drug Dictionary** (or an equivalent validated coding dictionary). Coding will be performed by trained data management personnel, under the oversight of clinical and medical staff to ensure accuracy and consistency.

27. Statistical methods

27a. Statistical methods used to compare groups for primary and secondary outcomes, including harms

All analyses will be performed on an intention-to-treat basis. For the primary outcome (incidence of shock within 48 hours of randomisation), proportions will be compared between the dextran and normal saline groups using the chi-square test or Fisher's exact test, as appropriate. Relative risks with 95% confidence intervals will be calculated. For continuous secondary outcomes, such as total intravenous fluid volume and duration of hospital stay, group comparisons will be made using the independent samples t-test or the Mann-Whitney U test, depending on data distribution. Time-to-event outcomes, such as time to first haemodynamic instability, will be analysed using Kaplan-Meier survival analysis with log-rank tests to compare groups. Repeated measures of haemodynamic parameters at multiple time points (1, 6, 12, 24, and 48 hours) will be assessed using mixed-effects linear or logistic regression models to account for within-subject correlation. Safety outcomes and harms, including fluid overload, acute kidney injury, and hypersensitivity reactions, will be summarised as frequencies and compared between groups using chi-square or Fisher's exact tests. All tests will be two-sided, and a p-value of <0.05 will be considered statistically significant.

27b. Definition of who will be included in each analysis (eg, all randomised participants), and in which group

All randomised participants will be included in the primary and secondary outcome analyses according to the intention-to-treat principle, analysed in the group to which they were originally assigned, regardless of protocol adherence or early discontinuation.

27c. How missing data will be handled in the analysis

Every effort will be made to minimise missing data through close monitoring and real-time data verification. For primary outcome analysis, missing outcome data will not be imputed. For secondary outcomes, if missing data exceed 5%, multiple imputation methods will be used assuming data are missing at random. Sensitivity analyses will be performed to assess the impact of missing data on study findings.

27d. Methods for any additional analyses (eg, subgroup and sensitivity analyses)

Prespecified subgroup analyses will be conducted based on age group (<40 vs ≥ 40 years), sex, and baseline

severity of plasma leakage. Sensitivity analyses will include per-protocol analyses excluding participants with major protocol deviations. No interim efficacy analyses are planned.

METHODS: MONITORING

28. Data monitoring committee

28a. Composition of the data monitoring committee

In this trial, we have formulated a data & safety monitoring committee (DSMC) responsible for safeguarding the interests of trial participants and assessing the safety and efficacy of the interventions throughout the trial. The DSMC consists of four members, two professors with extensive experience in conducting clinical research and two senior lecturers. The DSMC is independent of the investigators. The DSMC will review deidentified data for safety at four predetermined milestones (50, 100, 150, and 200 enrolled patients), but can require extra reviews at any time.

28b. Interim analysis and stopping guidelines

If an individual participant develops compensated or uncompensated shock or a clinically significant adverse effect related to the study drug, the study is terminated, and care is transferred to treating clinicians. However, if one group experiences shock or adverse effects at an uncharacteristically high frequency, the DSMC will be contacted immediately and asked for advice on modifying or terminating the trial. Unless group differences are observed that require unblinding (as determined by the DSMC), the DSMC will be blinded to treatment groups. After review, the DSMC will prepare a short report for the steering committee with recommendations on the continuation, modifications, or termination of the trial. The final decision on potential changes or termination will rest with the steering committee.

29. Trial monitoring

Trial monitoring will be conducted to ensure participant safety, protocol adherence, data integrity, and overall trial quality. A designated Data and Safety Monitoring Board (DSMB), independent of the study team, will oversee trial conduct and review interim safety and efficacy data at predefined intervals. On-site monitoring will be carried out by trained monitors who will verify informed consent procedures, eligibility criteria, adherence to randomisation, and correct implementation of the intervention protocols. Source data verification will be performed to confirm the accuracy of clinical records and case report forms, with special focus on primary and secondary outcome measures. Safety events, including adverse events and serious adverse events, will be reported in real time to the principal investigator and escalated to the DSMB and ethics committees as required. Protocol deviations will be documented and reviewed regularly to identify systemic issues, and corrective actions will be implemented promptly. The monitoring plan will follow International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines and institutional requirements, with regular progress reports submitted to the relevant ethics committees.

ETHICS

30. Research ethics approval

The protocol, participants' information forms, informed consent forms and all other study materials have been approved by the ethical review committees of the Faculty of Medicine & Allied Sciences, Rajarata University of Sri Lanka (ERC/2021/79), and the University of Peradeniya, Sri Lanka. Institutional approval has been obtained from the directors of the Teaching Hospital Anuradhapura and the Teaching Hospital Peradeniya.

31. Protocol amendments

All protocol modifications will first be discussed within the steering committee and then with all investigators. Once a consensus is reached, the co-principal investigators will communicate it to the ethics review committees. With the approval by the ethics review committees, the new amendments will be submitted to the Sri Lanka Clinical Trial Registry. Amendments will only be implemented after approval by the Sri Lanka Clinical Trial Registry. Amended protocols will then be handed over to all investigators and research assistants.

32. Consent or assent

32a. Who will take the consent

Investigators will remotely identify prospective participants by reviewing medical notes.
Potential participants will be invited to the study after being informed about it by a research assistant, who is a medical or nursing graduate outside the research team. Then they will be asked to read the information leaflet, which is available in all three languages used in Sri Lanka: English, Sinhala, and Tamil. Participants will be asked to summarise the procedure after reading the information leaflet and encouraged to ask questions. Finally, an independent observer will ask targeted questions to ensure the participant understands the information. If necessary, adequate time will be given to participants to discuss with family and friends. Participants will be clearly informed that they can withdraw from the study at any time on their own initiative, without giving reasons or explanation. Proxy consent will be obtained from participants with cognitive impairments. Capacity will be assessed by an

independent consultant using the MacArthur Competence Assessment Tool[17]. However, if decisional capacity is regained during the trial period, the participant's consent will be obtained again. If consent is rejected, they will be allowed to withdraw from the trial, and the clinical data collected will also be removed from analysis.

32b. Collection and use of participant data and biological samples for ancillary research.

This trial does not involve the collection of biological samples for ancillary or exploratory research purposes. All trial assessments will be based solely on clinical parameters, haemodynamic monitoring, and routine investigations performed as part of standard patient care. No additional biological sampling beyond standard clinical management will be undertaken. Therefore, participation in the study will not require any additional sampling or invasive procedures beyond standard clinical care, ensuring no added burden or risk to participants.

33. Confidentiality

Personal information about potential and enrolled participants will be handled with the highest level of confidentiality before, during, and after the clinical trial. At the time of screening and enrolment, only the minimum necessary identifying information (such as name, age, sex, and hospital number) will be collected to confirm eligibility and ensure appropriate clinical management. Once enrolled, each participant will be assigned a unique study identification code, and all trial-related data will thereafter be recorded and stored using this code rather than personal identifiers.

Access to identifiable information will be limited strictly to the investigators and designated study staff directly involved in patient care or data management. Data required for analysis, monitoring, or reporting will be deidentified before sharing with trial monitors, statisticians, ethics committees, or regulatory authorities. No personally identifiable information will be disclosed in any presentations, publications, or reports arising from the trial. Results will be published in aggregate form, ensuring that no individual participant can be identified.

All records will be securely stored in locked cabinets for paper files and password-protected, access-controlled databases for electronic data. After study completion, data will be archived in accordance with institutional policies and national regulations, ensuring long-term security while maintaining participant confidentiality. At all stages of the trial, safeguards will be in place to ensure that participants' personal information is protected and used only for the study.

34. Ancillary and post-trial care

Trial participants will have access to all ancillary care required during the trial period. Any adverse effects or complications due to trial participation will be promptly addressed at no cost. Ancillary care includes managing conditions that are not related to the trial participation but may arise during the trial period.

Post-trial care will be offered to all trial participants, especially those experiencing ongoing effects or complications from the trial interventions. They will have easy access to appropriate medical care and follow-up visits, ensuring continuity of care beyond the trial period.

Compensation for harm related to trial participation will be limited to providing medical care.

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