Trials

STUDY PROTOCOL

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Effectiveness of human albumin for clinical outcome in aneurysmal subarachnoid hemorrhages: a protocol for randomized controlled (HASH) trial

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Abstract

Background Aneurysmal subarachnoid hemorrhage (aSAH) is a dreadful acute neurological condition with an overwhelmingly high rate of associated morbidities and mortality. Despite leaping advancement in neurosurgical techniques and imaging modalities, there is no substantiative improvement in the overall prognosis for aSAH. Cerebral vasospasm remains the predominant cause of associated morbidities. Human albumin has been used in different neurological conditions, including head trauma, intracerebral hemorrhages, and ischemic strokes, with favorable outcomes. However, its beneficial use in aSAH has not been sufficiently explored until recently a published systematic review by our team. In view of the scarcity of published data and lack of robust evidence, our group has designed the first-ever RCT to compare the use of human albumin-enhanced fluid management versus standard fluid therapy with crystalloids in patients with aSAH.

Methods This single-center open-label, prospective, parallel group randomized control trial will be conducted at Hamad General Hospital, Doha, Qatar, from August 2024 to July 2027. A sample size of 84 (42 in each arm) has been calculated to be sufficient to detect a clinically significant difference in the modified Rankin scale good score between two groups (human-albumin induced volume expansion therapy versus crystalloid only) for fluid management in aneurysmal subarachnoid hemorrhage patients. The primary outcome will be based on a dichotomized modified Rankin scale [good grades (0–2) and poor grades (3–6)], while the secondary outcome will include symptomatic vasospasm, transcranial Doppler velocities, and Pulse index Contour Cardiac Output (PiCCO) parameters.

Discussion The trial aims to provide firsthand evidence on the beneficial use of human albumin to achieve an optimal fluid management regime to explore its potential role in improving clinical outcomes in patients with aSAH.

Trial registration ClinicalTrials.gov NCT06548477. Registered on August 9, 2024. https://clinicaltrials.gov/search?term=NCT06548477.

Keywords HASH trial, Human albumin, Subarachnoid hemorrhage, Aneurysmal, Effectiveness, Clinical outcome, Protocol

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Introduction

Background and rationale {6a}

Aneurysmal subarachnoid hemorrhage (aSAH) is a fatal neurological condition that may reach to a mortality of up to nearly 60% within 1 month of symptoms onset in untreated cases [1, 2]. Accounting for almost 5% of all stroke cases, aSAH predominantly affects the working age population with significant socioeconomic effect due to its impact on their quality of healthy life [3, 4]. Despite refined contemporary neurosurgical techniques and advancements in neurocritical care, secondary/delayed ischemia neurological deficits due to cerebral vasospasm have been implicated as the main contributing factor, related to poor clinical outcome in nearly 30% of the patients [5, 6]. Although, over the years, many different treatment modalities have been used to counter the detrimental effects of vasospasm including calcium channel blockers and triple-H therapy (hypervolemic, hemodilution, hypertension) with no substantiative improvement in clinical outcome and a search for an effective management strategy continues [7, 8].

In aSAH, hyponatremia due to increased release of natriuretic factors and reduction in intravascular volume has been attributed to cause clinical vasospasm and delayed ischemic neurological deficits as a part of natural course of the disease [9]. Reduced cerebral blood flow during aSAH has been explained based on two etiological factors [10]. Firstly, immediately with the clinical onset of aSAH, there is a generalized decrease in brain oxidative metabolism that contributes to drop in global cerebral blood flow (CBF) [9, 10]. This disruption in brain metabolic harmony is primarily caused by presence of toxic blood products in subarachnoid spaces although other contributing factors including acute hydrocephalus, brain edema, and rise in intracranial pressure may also play their roles to already compromised CBF [10]. Secondly, during the course of subsequent days to weeks when cerebral vasospasm sets in, it can further cause drop in CBF and cerebral metabolism [10]. This drop in CBF is topographically heterogenous in brain parenchyma and this manifests as the delayed cerebral ischemia causing neurological deficits [8, 10]. Based on these pathophysiological mechanisms, the standard use of hypervolemic therapy was rationalized in neurosurgical practice in the past to mitigate the detrimental effects of hypoperfusion and it used to be achieved by routine use of crystalloids/isotonic solutions and complementary colloidal agents including dextran, hypertonic saline, and human albumin in neurocritical care [11–14].

In animal studies with rat models for acute focal ischemia, albumin treatment has effectively reduced size of penumbra [15]. In contemporary clinical practice, the beneficial effects of human albumin has been investigated in cerebral strokes, acute brain injury, and intracranial hemorrhages, including aSAH with promising results [15–17]. In a pilot study conducted by Suarez et al. [14] (ALISAH) for a clinically safe dosage regimen for aSAH, it has also been observed that the use of albumin may be effective to prevent the deleterious effects of cerebral vasospasm by enhanced CBF leading to improvements in neurological outcome in aSAH patients [18–20]. Ali et al. [21] recently published a systematic review that highlighted obvious gaps in literature for the use of human albumin with no randomized control trial published to-date. This single center RCT will aim to investigate the potential beneficial role of human albumin to improve clinical outcome in patients with aSAH.

Objectives {7}

Primary objective: To evaluate the effectiveness of human albumin versus crystalloid-only fluid therapies for clinical outcome in patients with aSAH, based on dichotomized modified Rankin scale.

Secondary objective: To compare the effects of both modalities on the development of delayed cerebral ischemia (DCI), transcranial Doppler (TCD) velocities, and Pulse index Contour Cardiac Output (PiCCO) parameters with their daily monitoring for the use of human albumin versus crystalloid-only from day 4 till day 14 study period.

Trial design {8}

This is an open label, prospective, parallel group, exploratory, randomized control trial to investigate the potential beneficial role of human albumin to improve overall clinical outcome in patients with aSAH. A random assignment will be done with a ratio on one-to-one to either the intervention arm (with the use of human albumin plus crystalloid) or the control arm (standard therapy with crystalloid solution only) for fluid therapy in aSAH. The trial acronym is HASH (**H**uman **A**lbumin in **S**ubarachnoid **H**emorrhage) trial. The data will be analyzed based on intention-to-treat analysis. Figure 1 presents trial flow chart.

Methods: participants, interventions, and outcomes

Study setting {9}

This trial will be conducted at Hamad General Hospital, Doha, Qatar (primary research site). All included patients will be admitted to surgical intensive care unit (ICU) on presentation and will be managed according to standard protocol for management of subarachnoid hemorrhage for 2–3 weeks in ICU setting. Oversight will be provided by a research team comprised of investigators from neurosurgery department and surgical intensive

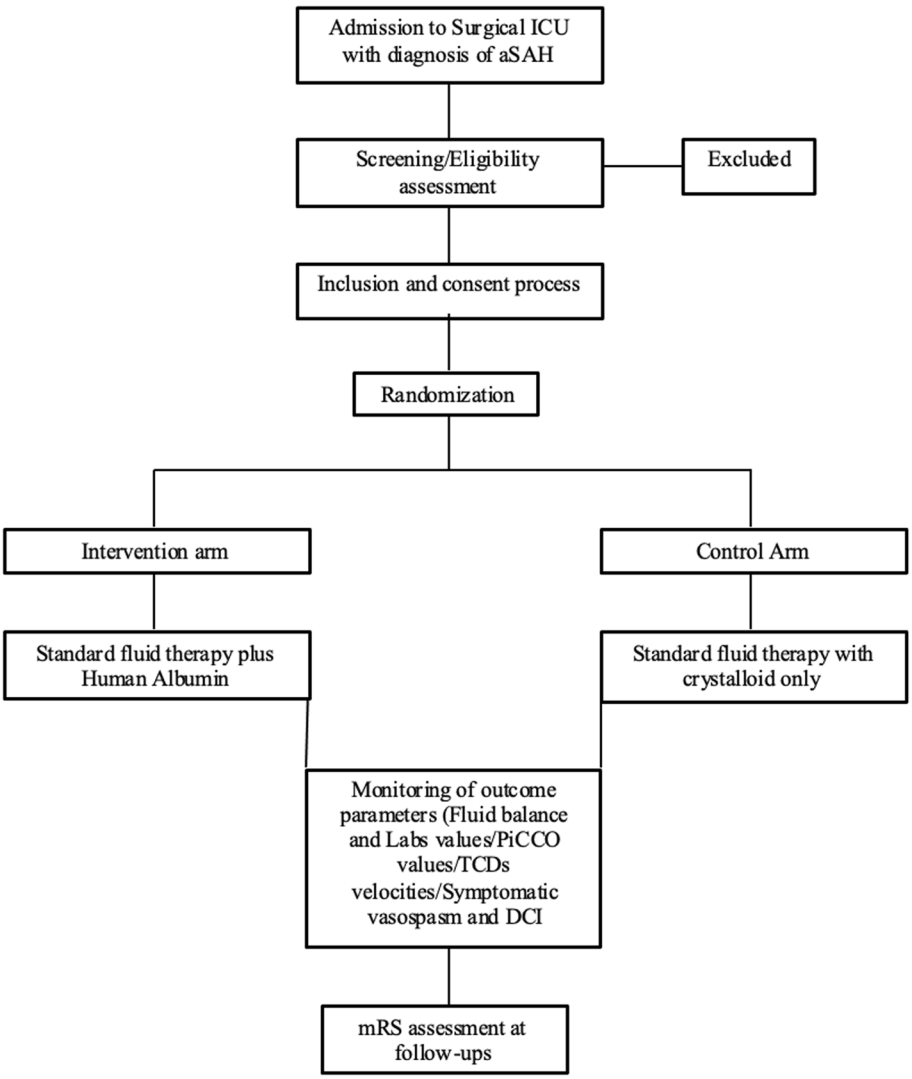

Fig. 1 Flow chart of trial

care unit-department of anesthesia. If patients are transferred to Qatar Rehabilitation Institute (QRI (secondary research site)) for neurorehabilitation as in-patient, they will be followed up by a member of research team (a staff from QRI team) and will be responsible for assessing the neurological status of patients at 3 months. If a patient is discharged from QRI before 3-month follow-up timeline, then patient will be followed up in neurosurgery outpatient clinic for documentation of final neurological status at 3 months.

Eligibility criteria {10}

All appropriate patients who are considered for HASH trial must fulfill criteria as outline below.

Inclusion criteria

- Age limits of participants will be between 18 and 80 years with either gender (male or female).
- Clinical presentation with the first of symptom of aSAH must be within 72 h before randomization.
- Clinical manifestation must be suggestive of aSAH that may include classical acute onset (thunderclap) headaches, changes in conscious level, neck rigidity, and neurological deficits.
- All cases with WFNS from grade 1 to 5 (at the time of randomization) will be recruited in the study.
- Head computed tomography demonstrates evidence of SAH (graded on Claassen's scale) [22].

- Diagnostic cerebral angiography shows a saccular aneurysm/s, consistent with clinical presentation of SAH.
- Definitive management of ruptured aneurysm/s (with microsurgical clipping or endovascular coiling or combined) must be carried out within 72 h prior to randomization.
- An informed consent by patient or surrogate representative must be duly signed and dated.

Exclusion criteria

- Timing of first symptom of SAH cannot be reliably ascertained.
- Cerebral angiogram negative SAH.
- Cerebral angiography showing mycotic/traumatic/fusiform aneurysm/s.
- Symptomatic vasospasm or angiographic (on TCD or CTA) sets in before recruitment within 72 h.
- History of clinical findings/hospitalization due to heart failure within past 6 months.
- Albumin administration prior to randomization in the same hospital admission.
- History of heart attack (acute myocardial infarct-MI) in last 3 months.
- Any clinical presentations or electrocardiography (ECG) findings suggestive of acute MI on current admission.
- Patient had clinical manifestations or ECG findings suggestive of 2nd or 3rd degree cardiac block or arrhythmias causing hemodynamic changes.
- Echocardiogram done before intervention/randomization showing an ejection fraction of < 40%.
- A creatinine level of more than 2.0 mg/dl and/or a creatinine clearance of less than 50 ml/min.
- IF patient is currently pregnant, lactating, or had delivery in past 1 month.
- Any allergies to any ingredient in human albumin preparation.
- A prior severe physical disability (mRS > 2) that may hamper assessment of clinical outcome.
- Advanced chronic obstructive pulmonary diseases (with FEV1 < 50%) may manifest as frequent episodes significantly affecting the overall quality of life.
- Hepatic failure or suspected liver dysfunction due to deranged liver functions, decreased serum albumin levels, high bilirubin levels with/without peripheral edema, and hepatic encephalopathy.
- Patient has been already enrolled in another study involving a drug administration.
- Patient suffering from terminal diseases with life expectancy < 6 months.
- If patient speaks any other language in which consent has not been translated.
- In case, patient drops out/withdraws from study or transferred out of state of Qatar and therefore lost to follow-up short of 3-month follow-up.

Who will take informed consent? {26a}

Prior to randomization, an assigned research team member will take an informed consent from the patient or an authorized surrogate. The assigned member will provide information face-to-face and will allow sufficient time for discussion to permit the treatment option. Consent will be translated in the most frequent languages (spoken, read, and written) in Qatar as per composition of population, including Arabic, English, Filipina, Urdu and Hindi, Malayalam, and Bangla. One copies of signed and dated informed consent with kept in patient records and another will be filed with trial documentation. If the patient is not competence enough to give consent due to the underlying neurological status, consent will be taken from the patient's legal representative. The legal representative/surrogate will be a person who is closely related to the patient who is her/himself fit and ready to consent on patient's behalf. The subject can decide to participate in study within 72 h (day 3) from onset of first symptoms of ictus as the intervention (albumin administration) will start from beginning of day 4. The subject will stay in the study until the last day of follow-up at 3 months from the date of informed consent taken. Subjects can withdraw consent without any obligation to inform/state reasons, any time after enrolment until the last follow-up.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable. All biospecimens will be covered under the routine management protocol of aSAH as practiced for all cases in the surgical ICU at our institution and no additional biological specimens are planned.

Interventions

Explanation for the choice of comparators {6b}

Fluid therapy is an important part for the management of aSAH to prevent and treat the manifestations of cerebral vasospasm. In contemporary neurosurgical practice, euvolemic fluid management is achieved with the use of crystalloid with/with addition of colloidal agents including human albumin. In an observational study, Suarez et al. [14] has reported that human albumin has potential beneficial role to improve clinical outcome of aSAH due to its diverse multifunctional mechanisms that ultimately lead to neuroprotective effects. This provides a rationale to explore the comparison of standard fluid therapy

Table 1 Target values for outcome parameters

Fluid balance and laboratory values		Hemodynamic and PiCCO values		Transcranial color Doppler	
Parameters	**Target values**	**Parameters**	**Target values (daily average)**	**Arteries**	**Mean velocities (cm/s)**
Fluid intake (L)	Varied	Heart rate (HR)	60–90 beats/min	Middle cerebral artery (MCA)	< 100
Fluid output (L)	Varied	Mean arterial pressure (MAP)	90–100 mm Hg	Anterior cerebral artery (ACA)	< 80
Fluid balance (ml)	± 500	Systolic blood pressure (SBP)	> 140 mm Hg	Terminal internal carotid artery (ICA)	< 100
Albumin intake (mg/kg)	1.25	Central venous pressure (CVP)	10–12 mm Hg	Posterior cerebral artery (PCA)	< 85 cm/s
Sodium level (mmol/L)	140–145	Stroke volume variation (SVV)	< 10%	Vertebral artery (VA)	< 60
Potassium level (mmol/L)	3.5–5.3	Extravascular lung water index (EVLWI)	< 10 ml		
GFR (ml/min)	> 60	Intrathoracic blood volume index (ITBVI)	850–1000 ml/min/m^2		
Hematocrit (%)	30–40	Global end-diastolic volume index (GEDVI)	680–800 ml/m^2		
Serum albumin level (g/L)	40–50	Systemic vascular resistance index (SVRI)	1700–2400 dyn-s/cm^5		
Serum magnesium level (mmol/L)	0.70–1.00	Cardiac index (CI)	3.0–5.0 L/min		
Serum osmolality (mOsm/kg)	275–295	Pulmonary vascular permeability index (PVPI)	1.0–3.0		
Serum creatinine (µmol/L)	60–106				
Serum phosphorus level (mmol/L)	1.12–145				
C-reactive protein (mg/L)	8–10				
Procalcitonin level (µg/L)	< 0.05				

with crystalloid alone (control arm) vs. with addition of human albumin (intervention arm) whether it has substantial influence on neurological outcome. A recently published systematic review by Ali et al. [21] underscores the paucity of published data on the use of human albumin in aSAH and therefore a formal RCT is a logical corollary for a robust evidence.

Intervention description {11a}

The onset of aSAH will be determined with timing of its first clinical manifestation at presentation. This time window will be used for initiation of treatment once 72 h is completed (beginning of 4th day post-ictus) and patient must have also received appropriate treatment for securing of the ruptured aneurysm/s before recruitment. In addition to standard fluid management protocol, patient in intervention arm will also receive intermittent boluses of 20% human albumin that will be administered with dosage regimen of 1.25 g/kg of body weight per 24 h. The total calculated dose/volume of albumin for the patient will be infused @ 34 ml/h (over 3 h) and will be divided in 3 boluses, spaced at 8-h intervals. Therefore, the 7-day study period will cover the duration of maximum cerebral vasospasm during natural course of aSAH. Albumin administration will be tailored according to the targeted values set for euvolemic fluid balance in each patient (Table 1). Before randomization (within 72 h post-ictus) and after day 10 (from day 11th to 14th), patient will only receive standard fluid therapy with crystalloid solutions.

Criteria for discontinuing or modifying allocated interventions {11b}

As albumin is derived from human blood, its side effects are extremely rare (< 1.1% as per manufacturer prescriptions guide). These adverse effects include anaphylaxis, skin reactions, flushes, hyperpyrexia, chills, nausea, vomiting, increase heart rate, and hypotension. However, these reactions disappear by slowing down or stopping the albumin infusion. Fluid overload or edematous reactions are reported commonly, depending on clinical status and infusion rate of albumin administration [23–26].

Strategies to improve adherence to intervention {11c}

A member of research team (co-principal investigator) in surgical ICU with study co-investigators will be responsible to oversee the adherence of all study parameters to study protocol from time of recruitment and throughout the hospital stay. The daily average values will be collected and will be entered timely in data collection sheet electronically. After patient is discharged, a designated research assistant will be in touch with patient/family to ensure their follow-up assessment at 3 months. In case patient is still in-patient in the neurorehabilitation facility, a member of research team from rehabilitation medicine will regularly assess the patient and will ensure follow-up evaluation.

Relevant concomitant care permitted or prohibited during trial {11d}

- Fluid management: All patients will receive a standard fluid regimen with normal saline 0.9% @ 1 ml/kg/min infusion. Patients in control group will only receive intermittent boluses of normal saline (300–500 ml) to maintain targeted parameters (Table 1). The aim for fluid administration is to keep patients in euvolemic fluid balance.
- Ionotropic support: Patient will receive inotropes (dopamine, norepinephrine, phenylephrine) if indicated to maintain mean arterial pressure (90–100 mm Hg) and/or systolic blood pressure (> 140 mm Hg) if volume-expansion therapy remains inadequate to achieve targeted parameters of fluid management.
- Nimodipine therapy: Nimodipine will be administered to all patients orally/through nasogastric tube and will be started on admission with dosage of 60 mg every 6 hourly.
- Seizure prophylaxis: All patients will receive prophylactic intravenous levetiracetam (Keppra®) with loading dose of 1 g followed by maintenance dose of 500 mg twice daily. Patients with aSAH has a high risk of 15.3% from the onset of ictus and prophylactic use of levetiracetam reduces this risk to as low as 3% [31, 32]. Seizures can result in additional insults to already suffering brain parenchyma and may contribute to acute neurological deterioration with worsening of overall prognosis [33]. Weighing risk–benefit for routine seizure prophylaxis, the balance goes in favor of its use and is currently a routine neurosurgical practice in most centers [34].
- Mineralocorticoid and hypertonic saline therapy: In patients with hyponatremia despite standard fluid management, fludrocortisone (starting with maximum dose 0.4 mg daily (titrated between 0.1 and 0.4 mg daily)) and hypertonic saline (2%) will be administered intermittently to achieve targeted sodium levels as per requirements and will be started if serum sodium level drops below 134 meq/L. In addition, hypertonic saline therapy can be incremented to 3% saline if there is difficulty improving or maintaining sodium level with 2% saline.

Provisions for post-trial care {30}

Not applicable to this trial as patient will only remain in study until the last follow-up at 3 months.

Outcomes {12}

Primary outcome

Primary clinical outcome will be based on dichotomized modified Rankin scale [good grades (0–2) and poor grades (3–6)] and will be measured on day 14 and at 3-month follow-up.

Secondary outcomes

Secondary outcomes will include symptomatic vasospasm with/without new onset infarctions on unenhanced computed tomography scan, transcranial Doppler velocities (daily values), and all PiCCO parameters (daily average values). On 14th day endpoint, a mean of all cumulative daily averaged values will be recorded for secondary outcome measures for (1) the study period (4th–10th day) and (2) subsequently without albumin therapy (from day 11th to 14th day) on day 14 endpoint. These secondary outcome measures will be compared between study arms to assess difference in the effect size of the intervention.

Participant timeline {13}

A detailed timeline displayed in Fig. 2 as per SPIRIT guidelines (https://spirit-statement.org/publications-downloads/) [35].

Sample size {14}

A sample size of 84 patients, 42 in each group, has been calculated as sufficient to detect a clinically important effect size difference of 29% in mRS good score at 3 months between two groups (human-albumin induced volume expansion therapy versus crystalloid only) for fluid management in aSAH patients using a two-tailed *z*-test of proportions/chi-square test with 80% power and a 5% level of significance. This 29% difference represents a 68% mRS good score at 3 months among patients receiving albumin and 29% among patients receiving non-albumin group in a previously conducted observational study [14]. As per our institutional admission statistics,

	STUDY PERIOD					
	Enrolment	Allocation			Post-allocation (Follow-up)	
	Day 1-3		4th day	10th day	Day-14	3-month
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
INTERVENTIONS:						
Intermittent Albumin administration			●	●		
ASSESSMENTS:						
Delayed Cerebral Ischemia (DCI)			●	●	●	
Transcranial Doppler velocities			●	●	●	
PiCCO parameters			●	●	●	
Modified Rankin Scale			●			●

Fig. 2 Schedule of enrolment, interventions, and assessments

we expect 40 patients per year and this number will be sufficient to reach our sample size in 3 years, factoring in a 10% drop rate.

Recruitment {15}

All patients with aSAH are admitted to surgical ICU and will be screened for eligibility (Fig. 1). Patients will enter the trial on the beginning of day 4 (after 72 h) post-ictus and after definitive treatment of the ruptured aneurysm/s (either by microsurgical clipping or neuro-interventional techniques or combined and in all cases, this will be done within 72 h post-ictus but before randomization). The rationale to use 4th–10th day period for albumin administration is based on the well-established fact in contemporary neurosurgical practice that cerebral vasospasm usually occurs between day 4 and day 14 post-ictus, with its peak on day 7 [29–31]. The albumin therapy from day 4 to day 10 (7-day period) will cover the peak duration of cerebral vasospasm.

Assignment of interventions: allocation

Sequence generation {16a}

The block randomization method will be used to assign subjects to two groups [A: intermittent human albumin along with standard crystalloid fluid administration (intervention arm) versus B: standard crystalloid fluid therapy (except human albumin) for euvolemic fluid therapy (control arm)]. Blocking is a method of restricted randomization that ensures both groups are balanced at the end of every block. A total of 84 patients will be randomized into 42 blocks with two permuted blocks of 2 (AB and BA).

Concealment mechanism {16b}

Sealed opaque envelopes will be used to avoid any potential tempering or disclosure of identifiers to conceal the sequence until the patient is assigned to a randomized study group.

Implementation {16c}

The coded list of randomization numbers with assigned study groups will be kept secured and will only be accessible to PI-designated research team members who will ensure the concealment of patients to assigned treatment arms (using sequentially number opaque and sealed envelopes).

Assignment of interventions: blinding

Who will be blinded {17a}

Only participants will be blinded while research team members, care providers, and outcome assessors will be aware of the assigned treatment group.

Procedure for unblinding if needed {17b}

Unblinding will be allowed in case of emergency situation to avoid harm to participants and this is likely if participants develop any adverse reactions from the use of human albumin. In such situations, assigned code may be disclosed to participants/legal representatives and excluded.

Data collection and management

Plans for assessment and collection of outcome {18a}

Screening, eligibility assessments, and recruitment

- All admitted patients with initial working diagnosis of aSAH (in surgical ICU) will be screened as per trial eligibility criteria and patients excluded will also be recorded in screening logs.
- Once eligibility is established, an informed consent face-to-face (in patients' native spoken language) will be initiated by assigned research team member/s and will be signed and dated by patient or his/her legal representatives as per hospital protocol.
- Aneurysmal SAH will be documented by an unenhanced CT scan or evidence of CSF xanthochromia (lumbar puncture) on admission.
- Definitive diagnosis of ruptured aneurysm will be established on catheter cerebral angiography.
- Day 1 of SAH will begin with start time of first clinical manifestation of ictus and will determine the time window period before the randomization on day 4. During this time period of 72 h, patient will undergo screening, eligibility assessment, consent process, and treatment allocation.
- Baseline neurological evaluation will be done by neurosurgery and intensive care teams in surgical ICU and a WFNS grade will be documented by a board-certified neurosurgeon once the eligibility of patient is established.
- The extent of SAH on CT scan brain will be documented based on grading system as proposed by Claassen et al. [22] CT scan will be discussed by a research team member (a board-certified neurosurgeon) with a neuroradiologist to have a consensus of graded findings.
- Patients will enter the study on the beginning day 4 (after 72 h) once aneurysm/s is secured within 72 h post-ictus before randomization.
- Demographic parameters and laboratory tests will be collected as per data collection sheet before registering the patient in the study as a baseline data.
- All variables related to fluid balance (intake/output), albumin intake, PiCCO parameters, and lab investigations (electrolytes, serum creatinine, GFR, hematocrit, serum albumin level, etc.) will be monitored and recorded on daily basis. A baseline data will recorded within 72 h before albumin administration and then throughout study period of 7 days (between day 7 and day 10) as well as post-intervention until day 14th (from day 11 to day 14).

Intervention phase

- All patients will receive a standard fluid regimen with normal saline 0.9% at the rate of 1 ml/kg/min. Patients in control group will only receive intermittent boluses of normal saline to maintain targeted parameters (Table 1). The aim for fluid administration will be to keep patients in euvolemic fluid balance.
- Patients in intervention arm will also receive intermittent boluses of 20% human albumin (in addition to standard fluid therapy) that will be administered with dosage regimen of 1.25 g/kg of body weight per 24 h. The maximum total calculated dose/volume of albumin for the patient will be infused @ 34 ml/h (over 3 h) and will be divided in 3 boluses, spaced at 8-h intervals. During intervention period, the 7-day study period will cover the peak period of cerebral vasospasm from day 4th until 10th day. Albumin administration will be tailored according to the targeted values set for euvolemic fluid balance in each patient.
- Before randomization (within 72 h post-ictus) and after day 10 (from day 11th to 14th), patient will only receive standard fluid therapy.

Assessment and monitoring (for fluid balance and vasospasm)

- Systemic hemodynamics will be monitored from 4 to 14th day using transpulmonary thermodilution system (PiCCO Plus™). A PiCCO catheter (Pulsion Medical Systems®) will be inserted into the brachial or femoral artery, and a central venous line will be inserted into the superior vena cava. Both catheters will be connected to the PiCCO Plus for continuous monitoring of cardiac output, contractility, pre- and afterload. Transpulmonary thermodilution will be measured continuously to monitor volume management and lung water and an average of all daily values will be used to aim for targeted values. Thermodilution curves according to the Stewart–Hamilton principle will be recorded from the PiCCO catheter to allow estimations of global

Table 2 Grading of vasospasm severity based on TCD mean flow velocities

Vasospasm grades	MCA	ACA	ICA	PCA	VA
Mild	120–149	80–119	100–149	> 85	70–85
Moderate	150–200	120–150	150–200		86–100
Severe	> 200	> 150	> 200		> 100

end-diastolic volume index (GEDVI; normal range, 680–800 ml/m^2), extravascular lung water index (EVLWI; 3.0–10.0 ml/kg), pulmonary vascular permeability index (PVPI, 1.0–3.0), stroke volume variation (SVV; < 10%), intrathoracic blood volume index (ITBVI; 850–1000 ml/min/m^2), and systemic vascular resistance index (SVRI; 1700–2400 dyn·s/cm^5 per square meter). Cardiac function will be evaluated on the basis of cardiac index (CI; 3.0–5.0 L/min per square meter). These targeted values (Table 1) will aim to maintain euvolemic fluid balance as a standard contemporary fluid management strategy that correlates with optimized brain tissue oxygenation and cerebral blood flow to prevent vasospasm in aSAH [36–39].

- Transcranial Doppler ultrasound will be used as a standard tool (done by a trained technician) for daily monitoring of velocities of major cerebral arteries of circle of Willis for assessment of vasospasm on both sides. Thresholds for development of vasospasm (based on mean arterial flow velocities) will be > 120 cm/s (middle cerebral arteries), > 100 cm/s (ICA), > 80 cm/s (anterior cerebral arteries), > 85 cm/s (posterior cerebral arteries) (> 85 cm/s), and > 70 cm/s (vertebral arteries) and vasospasm will be categorized as mild, moderate, and severe in each artery (Table 2) [27, 40]. Baseline values before just randomization into the study and then daily values will be recorded from 4 to 14th day post-ictus.
- If there are any findings suggestive of cerebral vasospasm based on TCD screening in context of clinical suspicion, further specific investigations will be done using CT angiography and CT perfusion as per protocol for the management of aSAH at HMC. In all confirmed cases of vasospasm on CT angiography/CT perfusion, patients will undergo formal catheter angiography for pharmacological angioplasty (with intraarterial nimodipine/milrinone).
- In this trial, delayed cerebral ischemia (DCI) will be used as a standard nomenclature to avoid other similar terms [delayed ischemic neurological deficits-DINDS, delayed ischemic deficit, delayed neurologic deficit, secondary cerebral ischemia, clinical vasospasm, symptomatic vasospasm, symptomatic ischemia, and cerebral ischemia, delayed ischemic neurological deficits (DINDs)] that are used for this clinical phenomenon in published literature.
- The standard definition of DCI adopted from literature will be used in this trial as:
- "The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least one hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes (e.g., rebleeding, hydrocephalus, edema, electrolyte disorder, infection, or seizures) by means of clinical assessment, on CT or MRI scanning of the brain, and appropriate laboratory studies" [27, 28]. New-onset infarctions will be defined as newly appeared focal areas of hypodensities on repeat CT scan brain done (not seen on pre-randomization CT scans) during the study period or at follow-up.

Plans to promote participant retention and complete follow-up {18b}

- Depending upon clinical conditions, patients will be transferred out of surgical ICU to neurosurgical floor for further management after 14 days as per clinical conditions.
- Patients will be discharged home or transferred to rehabilitation facility (secondary research site) once fit to be discharged/transferred from acute care service from HGH (primary research site).
- Patient will be followed up at 3 months in outpatient clinic (if patient discharged home) or at rehabilitation facility (if still in-patient) to record the final outcome parameters at 3 months.

Data management {19}

- All patient identifiers will be coded and any link between code and identifier will be deleted at the end of the data collection and anonymized data will be kept for at least 5 years after study completion.
- The linking sheet to the subject's identifier will be kept in a secure locked place in the dedicated research office cupboard.

- Electronic data will be stored in our institutional computer, dedicated to this research and will be password protected.
- Hard copy of data collection sheet (manually filled) will be kept in locked and only principal investigator will control access to data.
- In compliance with Good Clinical Practice (GCP) guidelines, all relevant documentation about clinical trial (signed and dated patient consent forms, IRB approval letters, and other related materials) will be kept in record for 5 years past conclusion of this RCT.

Confidentiality {27}

All patients' identifiers will be coded to strictly prohibit any kind of identification of participants. Any link between codes and identifiers will be deleted at the end of the data collection and anonymized data will be kept for at least 5 years after study completion. All appropriate measure will be implemented to maintain a confidential record of personal medical data.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable as all laboratory tests and biospecimens are collected routinely for all patients as a part of standard management protocol for aSAH in the surgical ICU at our institute.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Descriptive and inferential statistics will be used to characterize the study sample and test hypotheses. A Shapiro–Wilk test will be used, and histograms and normal probability/normal-quantile plots will be examined to verify the normality of distribution of continuous variables. Descriptive results for all continuous variables (e.g., age) will be presented as mean ± standard deviation (SD; for normally distributed data), or median with inter-quartile (25th–75th percentiles) range (for data not normally distributed), while numbers (percentage) will be reported for all categorical variables (e.g., gender). The primary objective is to compare the mRS score (good vs. poor) at 14th day and at 3 months between two groups (patients receiving albumin versus non-albumin) for fluid management in aSAH patients, which will be done using Pearson chi-square test or Fisher exact test as appropriate. Odds ratio and 95% confidence interval will be reported. Bivariate analysis will be performed using independent sample *t*-test, Mann–Whitney *U* test, Pearson chi-square test, or Fisher exact test whenever appropriate to compare all the demographic (e.g., age, gender) and clinical characteristics (e.g., delayed cerebral ischemia/new-onset infarctions, PiCCO parameters, and transcranial Doppler velocities) between the two groups for mean of the cumulated value at day 14th of follow-up.

Binary logistic regression will also be used to assess the relationship between all the demographic and clinical characteristics with mRS score at 14th day and 3 months. Odds ratio and 95% confidence interval will be reported. Multiple binary logistic regression models will be used to identify significant independent factors (e.g., albumin vs. non-albumin) associated with mRS score at 3 months after adjusting for potential confounders (e.g., sex, age, comorbidities). Wald test will be used on each factor to determine which factors are significant. Adjusted odds ratio (AOR) and 95% confidence interval for the AOR will be reported. Statistical significance will be set at "P" < 0.05 (two-tailed). Hosmer–Lemeshow will be used to assess the model's goodness-of-fit. All the analysis will be performed using Statistical Package for Social Sciences version 29 (SPSS).

Interim analyses {21b}

An interim analysis is scheduled to occur once the trial has successfully recruited at least half of the intended sample size, comprising 42 patients distributed evenly across the two study arms. Should the results indicate a significant skew in favor of or against the use of albumin, the steering committee will make a determination regarding the continuation or cessation of the trial, taking into consideration the interim findings.

Methods for additional analyses (e.g., subgroup analyses) {20b}

No subgroup analyses are planned for this trial.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Participants who fail to complete follow-up for 3 months will be excluded from data analyses.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

Not applicable as no data will be shared, related to statistical codes or patient identifiers.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

Medical research center (MRC) and clinical trial unit (CTU) provide oversight on all the RCTs conducted at Hamad Medical Corporation. An independent data

monitoring committee from MRC, at Hamad Medical Corporation, will scrutinize the safety of participants. The committee members will conduct periodic evaluations of accumulated data and will advise the research team about the conduct of study with/without modifications or implementation any amendments or terminate the study accordingly.

Composition of the data monitoring committee, its role and reporting structure {21a}

Data monitoring team will compose of research team members PI (Ali A) and two co-PIs (Khan M and Shaikh N) who will monitor smooth conduct of trial with collection of all variables and ensure the collection of all clinical outcome parameters at follow-up and will be responsible to report any adverse effects and submission of progress report. This team will be having periodic visit from a supervising committee from MRC and CTU staff who ensure the trial is complying to approved protocol version.

Adverse event reporting and harms {22}

Anaphylactic reactions and volume overload are the main adverse effects that will be closely monitored by assigned nurse in intensive care setting throughout the IV demonstration of human albumin. In addition, patients will be regularly monitored every hour for development of any adverse drug reaction (ADR) during and post-infusion period throughout the study period. In case of any adverse reaction, the assigned nurse will inform ICU physician, and s/he will take immediate appropriate measures according to each adverse reaction developed. All side effects will be tracked throughout fluid management therapy of study period with appropriate documentation on a pre-designed ADR form and will be reported to IRB accordingly as per regulations.

Frequency and plans for auditing trial conduct {23}

At Hamad Medical Corporation, medical research center oversees all research activities and has a designated committee of experts that play a key role for overseeing the conduct of all clinical trials and provide guidance for preparation of trial proposals with emphasis on ethical aspects and research methodology. During the conduct of this RCT, this committee will conduct a yearly visit to monitor adherence to protocol and scrutinize the conduct of the study, facilitating in solving the issues related to quality. The committee will also peruse the preparation of the final report ensuring that the conclusion of this trial is compiled and aligned with trial data.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committee) {25}

If required during the conduct of this trial, the research proposal can be amended to guide the future steps in research process. All amendments in revised protocol will be in compliance with GCP guidelines and must have an approval from IRB before implementation. These amendments will be reported to IRB at MRC and CTU accordingly as per regulations.

Dissemination plans {31a}

The trial results will be disseminated through publication in relevant research journals. In compliance with local regulations, the study protocol may be submitted to all relevant clinical trial registries (such as ClinicalTrials.gov). The final results and interpretation will also be presented on relevant medical forums. The authorship will be determined in compliance with guidelines from MRC.

Discussion

Khan et al. [29] conducted a 10-year epidemiological study (2007–2016) of aSAH patients in Qatar and reported an annual incidence of 0.9–2.3 per 100,000 of population. The in-hospital mortality remained comparatively higher 21.2% with cerebral vasospasm being the most significant factor [28, 36]. We hypothesize that the use human albumin has potential to improve overall prognosis in patients with aSAH and this will have an impact for better clinical outcome. In addition, this trial will be able to provide a firsthand evidence for the use human albumin in aSAH patients and will also provide substantive evidence for improved clinical outcome.

Suarez et al. [14] reported in his observational study that the use of human albumin in aSAH may have a beneficial role in decreasing the incidence of cerebral vasospasm with better neurological outcome and this could possibly be attributed to its implicit neuroprotective properties. Different mechanisms have been suggested for its potential role in exerting neuroprotective actions that includes (1) regulation of intracellular calcium ionic density; (2) changes in arachidonic acid concentration and membrane fluidity; (3) impediment in programmed cell death; (4) manipulation in metabolism of nitric oxide; (5) enhancing glutathione concentration that regulates the redox signals in cellular antioxidation; and (6) blockage of adhesion molecular expression [14, 40–44]. It is uncertain which of these mechanisms could play a predominant role for providing this neuroprotective role. However, it likely that this effect is the end-product of a combination of all these biochemical interactions. Irrespective of underlying complex mediation of these

cellular mechanisms, it is the ultimate effect of human albumin on the neural endothelium that may be contributing to mitigation in the development of cerebral vasospasm. In the context of these multifactorial mechanisms operating in development of cerebral vasospasm, it is logical to use a multifunctional neuroprotective agent like human albumin in these patients and thereby providing a rationale to explore this potential property in aSAH with an appropriately designed clinical trial.

Trial status

Protocol version: 1.1.
Approval date: 18th July 2024.
Recruitment start date: 1st August 2024.
Trial end date (anticipated): 31st July 2027.

Abbreviations

aSAH	Aneurysmal subarachnoid hemorrhage
CI	Cardiac index
CT	Computed tomography
CTU	Clinical trial unit
DCI	Delayed cerebral ischemia
DIND	Delayed ischemic neurological deficits
EVLWI	Extravascular lung water index
GEDVI	Global end-diastolic volume index
HASH	**H**uman **A**lbumin in Subarachnoid **H**emorrhage
ITBVI	Intrathoracic blood volume index
mRS	Modified Rankin scale
MRC	Medical research center
PiCCO	Pulse index Contour Continuous Cardiac Output
PVPI	Pulmonary vascular permeability index
SAH	Subarachnoid hemorrhage
SVRI	Systemic vascular resistance index
SVV	Stroke volume variation
TCD	Transcranial Doppler
WFNS	World Federation of Neurological Surgeons

Acknowledgements
Not applicable.

Authors' contributions {31b}
Ali A has been the principal investigator (PI) for this trial and has orchestrated the planning for the trial. All other authors have played significant roles in conduct of this trial as assigned by PI. This study proposal manuscript is drafted by PI and has been reviewed and approved by all authors.

Funding {4}
This study trial has internal funding from the Medical Research Center with MRC No. 01–24-229.

Data availability {29}
Anonymized data will be kept for at least 5 years after study completion as per IRB regulations for clinical trials. Only principal investigator and his designees will control access to trial data.

Declarations

Ethics approval and consent to participate {24}
The ethics committee approval received from the local IRB. Informed consent duly signed and dated from each participant is obligatory as IRB regulations.

Consent for publication {32}
Consent for publication is not applicable as no patient data is being disclosed.

Competing interests {28}
The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices, being used in this trial.

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