Title

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Journal

BMJ Open, 13(11)

ISSN

2044-6055

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Publication Date

2023-11-01

DOI

10.1136/bmjopen-2023-078713

BMJ Open

Angiotensin II in liver transplantation (AngLT-1): protocol of a randomised, double-blind, placebo-controlled trial

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To cite: Bokoch MP, Tran AT, Brinson EL, *et al*. Angiotensin II in liver transplantation (AngLT-1): protocol of a randomised, double-blind, placebo-controlled trial. *BMJ Open* 2023;**13**:e078713. doi:10.1136/bmjopen-2023-078713

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-078713).

Received 09 August 2023
Accepted 24 October 2023

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ABSTRACT

Introduction Catecholamine vasopressors such as norepinephrine are the standard drugs used to maintain mean arterial pressure during liver transplantation. At high doses, catecholamines may impair organ perfusion. Angiotensin II is a peptide vasoconstrictor that may improve renal perfusion pressure and glomerular filtration rate, a haemodynamic profile that could reduce acute kidney injury. Angiotensin II is approved for vasodilatory shock but has not been rigorously evaluated for treatment of hypotension during liver transplantation. The objective is to assess the efficacy of angiotensin II as a second-line vasopressor infusion during liver transplantation. This trial will establish the efficacy of angiotensin II in decreasing the dose of norepinephrine to maintain adequate blood pressure. Completion of this study will allow design of a follow-up, multicentre trial powered to detect a reduction of organ injury in liver transplantation.

Methods and analysis This is a double-blind, randomised clinical trial. Eligible subjects are adults with a Model for End-Stage Liver Disease Sodium Score ≥25 undergoing deceased donor liver transplantation. Subjects are randomised 1:1 to receive angiotensin II or saline placebo as the second-line vasopressor infusion. The study drug infusion is initiated on reaching a norepinephrine dose of 0.05 µg kg^{-1} min^{-1} and titrated per protocol. The primary outcome is the dose of norepinephrine required to maintain a mean arterial pressure ≥65 mm Hg. Secondary outcomes include vasopressin or epinephrine requirement and duration of hypotension. Safety outcomes include incidence of thromboembolism within 48 hours of the end of surgery and severe hypertension. An intention-to-treat analysis will be performed for all randomised subjects receiving the study drug. The total dose of norepinephrine will be compared between the two arms by a one-tailed Mann-Whitney U test.

Ethics and dissemination The trial protocol was approved by the local Institutional Review Board (#20–30948). Results will be posted on ClinicalTrials.gov and published in a peer-reviewed journal.

Trial registration number ClinicalTrials.gov NCT04901169

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Double-blind, randomised controlled trial design.
⇒ Precise titration protocol.
⇒ Exclusion criteria designed to maximise safety and minimise risk of adverse drug effects.
⇒ Results may not be generalisable to patients undergoing liver transplantation with Model for End-Stage Liver Disease Sodium Score <25 or those with acute liver failure.
⇒ Results may not be generalisable to patients undergoing living-donor liver transplantation or simultaneous liver and kidney transplantation.

INTRODUCTION

Vasoplegia is low systemic vascular resistance with normal or high cardiac output despite the use of high doses of vasopressors.[1 2] This syndrome frequently arises during liver transplantation (LT), particularly in patients with high Model for End-Stage Liver Disease Sodium (MELD-Na) scores and those requiring preoperative renal replacement therapy (RRT).[3] High doses of the catecholamines norepinephrine (NE) and epinephrine are typically infused to maintain adequate mean arterial pressure (MAP) and organ perfusion.[4 5] However, extreme doses of catecholamines may impair microvascular perfusion to the kidneys and other organs[6 7] or trigger arrhythmias.[8] Rescue therapies for vasoplegia are limited to the off-label use of methylene blue or hydroxocobalamin.[9] New haemodynamic therapies are needed to reduce the high rate of acute kidney injury (AKI) after liver transplant, seen in 50%–80% of cases. Acute kidney injury after LT significantly reduces patient and graft survival.[10–12] Reducing catecholamine dose by adding a vasopressor with a different mechanism may help improve renal perfusion pressure and reduce postoperative AKI after LT.

The peptide vasopressor angiotensin II (AngII) was approved by the US Food and Drug Administration in 2017 for use in vasodilatory shock. Angiotensin II causes vasoconstriction by activating the angiotensin

II type 1 G protein-coupled receptor in arterial smooth muscle, which is distinct from the catecholamine receptors. Angiotensin II selectively constricts efferent arterioles in the kidney to maintain or improve glomerular filtration rate.[6] In ATHOS-3, a large, multicentre, international, randomised clinical trial (RCT) of patients with vasodilatory shock (mostly due to sepsis), AngII infusion increased the blood pressure of patients already receiving doses of NE greater than 0.2 µg kg^{-1} min^{-1}.[13] Posthoc analyses of the ATHOS-3 trial found improved 28-day survival, greater blood pressure response and earlier liberation from RRT in patients receiving AngII who required RRT at the time of drug initiation[6] or who had serum renin levels above the median.[14] These results suggest that AngII may reduce the required dose of traditional vasopressors and improve microcirculatory flow to organs, especially the kidneys.[15] Successful use of AngII infusion for vasoplegia during LT has been reported.[16] However, no RCTs of AngII have been completed in this setting.

Angiotensin II therapy is of particular interest for patients undergoing LT not only due to the frequency of vasoplegia observed during LT but also because of the mechanism of action of AngII. The renin-angiotensin system is known to be altered in cirrhosis and contributes to the pathophysiology of end-stage liver disease. The renin-angiotensin system contributes to progression of hepatic fibrosis, portal hypertension and derangements in sodium and volume regulation.[17 18] Elevated plasma renin is observed after cardiopulmonary bypass and provides specific rationale for administering AngII in cardiac surgery.[19–21] A similar rationale may hold for LT. We report the protocol for a randomised, double-blind, placebo-controlled trial of AngII as the second-line vasopressor during LT in patients with MELD-Na Score ≥25.

OBJECTIVES

The primary objective of the AngLT-1 Trial is to assess the efficacy and safety of AngII infusion during LT. Efficacy is assessed by the intraoperative dose of NE required to maintain a MAP ≥65 mm Hg. Safety is assessed by predefined adverse events. The secondary objective is to measure secondary outcomes such as the incidence of AKI and liver graft dysfunction. These data will allow for the design and initiation of a subsequent multicentre RCT powered to detect improvement in postoperative outcomes.

METHODS AND ANALYSIS

Eligibility criteria

Inclusion criteria are shown in box 1. Eligible subjects are adults (aged ≥18 years) undergoing LT from a deceased donor with a calculated MELD-Na Score ≥25 at the time of transplant (MELD 3.0 was released after this trial was initiated and therefore eligibility is determined by MELD-Na). Subjects also require NE infusion at a dose >0.05 µg kg^{-1} min^{-1} during LT before study drug is initiated. At the University of California, San Francisco, over 80% of patients meeting the inclusion criteria receive norepinephrine infusions above the threshold of 0.05 µg kg^{-1} min^{-1} during LT. The exclusion criteria are intended to minimise variability in procedural complexity, expected surgery length and intraoperative vasopressor requirements (box 1). Patients with cardiac conditions that could theoretically be harmed by intense vasoconstriction from AngII are excluded. Finally, because the US Food and Drug Administration label for AngII includes a warning about increased risk of venous and arterial thromboembolism, patients with a history of thrombosis, inherited hypercoagulable disorder or conditions increasing the risk of hepatic artery thrombosis (eg, coeliac stenosis) are excluded.

Box 1 Eligibility criteria.

Inclusion criteria
- ⇒ Age ≥18 years
- ⇒ Undergoing LT from a deceased donor
- ⇒ Calculated MELD-Na Score ≥25 at the time of transplant
- ⇒ Require norepinephrine infusion at a dose >0.05 µg kg^{-1} min^{-1} during LT before study drug is initiated

Exclusion criteria

Type of liver transplantation
- ⇒ Living-donor liver transplantation
- ⇒ Donation after cardiac death without normothermic machine perfusion
- ⇒ Acute liver failure
- ⇒ Listed for or receiving simultaneous liver-kidney transplantation
- ⇒ Liver re-transplantation
- ⇒ Split liver transplantation (isolated right or left lobe)

Cardiac conditions
- ⇒ Portopulmonary hypertension (defined as mean pulmonary artery pressure >20 mm Hg, pulmonary vascular resistance ≥3 Woods Units, and pulmonary artery wedge pressure ≤15 mm Hg in the setting of portal hypertension without another known cause).
- ⇒ Left ventricular systolic dysfunction (defined as ejection fraction <45%)

Thromboembolic risk
- ⇒ History of thrombotic or embolic disease, inherited hypercoagulability disorder or therapeutic anticoagulation
- ⇒ Portal vein thrombosis
- ⇒ Coeliac stenosis
- ⇒ History of Raynaud's disease

Other
- ⇒ Preoperative treatment with an angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor (within 48 hours before LT)
- ⇒ Active bronchospasm at the time of LT
- ⇒ End-stage renal disease (chronic estimated glomerular filtration rate <15 mL min^{-1} 1.73 m^{-2} or chronic renal replacement therapy)
- ⇒ Known history of allergy to synthetic human angiotensin II
- ⇒ Subject intubated and/or mechanically ventilated prior to entering the operating room for LT

LT, liver transplantation; MELD-Na, Model for End-Stage Liver Disease Sodium.

Intervention

Except for the study drug and vasopressor management protocol, perioperative care is provided in accordance with local protocols. Invasive monitoring of radial artery

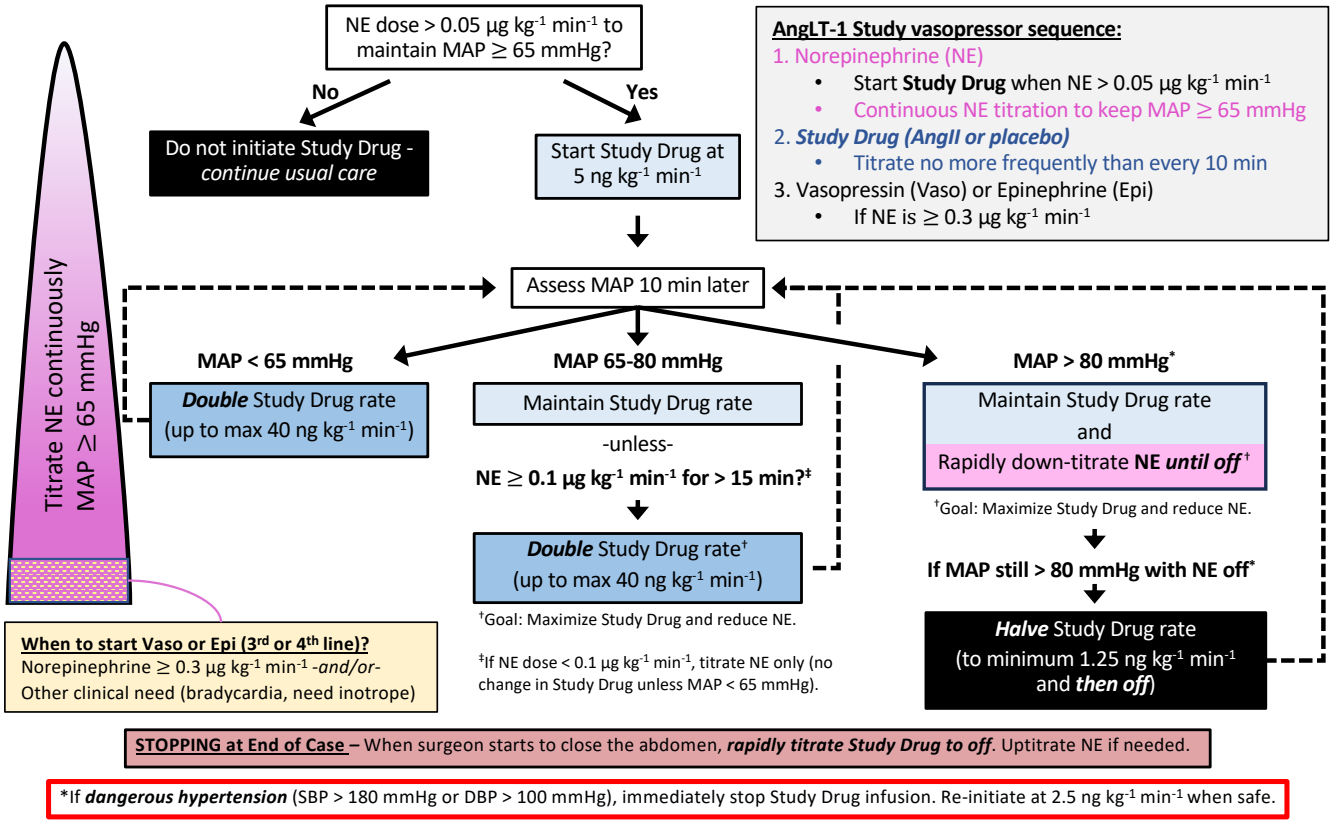

Figure 1 Study drug initiation and titration protocol. NE, norepinephrine; MAP, mean arterial pressure; NE, norepinephrine; AngII, angiotensin II; SBP, systolic blood pressure; DBP, diastolic blood pressure.

and central venous pressures is performed. Pulmonary artery catheters are not routinely used at our centre. Non-invasive cardiac output monitoring (LiDCO, Masimo, Irvine, CA, USA) is used when available. Norepinephrine is initiated as the first-line vasopressor for all subjects. Once the NE infusion dose exceeds 0.05 µg kg^{-1} min^{-1}, the study drug infusion is initiated at a rate equivalent to 5 ng kg^{-1} min^{-1} of AngII. The study drug is delivered through a dedicated port of a central venous catheter that is routinely placed as part of standard anaesthesia care. The study drug infusion is connected in a y-configuration to a 0.9% saline carrier running at 50 mL h^{-1} throughout surgery to ensure rapid delivery of any dose changes.

The study drug infusion is titrated no more frequently than every 10 min between 1.25 ng kg^{-1} min^{-1} and 40 ng kg^{-1} min^{-1} according to the protocol (figure 1). In between study drug titrations, the anaesthesiologist continuously titrates NE as frequently as needed to maintain a MAP ≥65 mm Hg. If the MAP is persistently >80 mm Hg, the anaesthesiologist will downtitrate NE first and then down-titrate the study drug. If at any time the subject's blood pressure rises to an unsafe level (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mmHg), the anaesthesiologist immediately stops the study drug infusion and resumes at a lower rate when safe.

The titration protocol guides the anaesthesiologist to use only NE and study drug infusions until the NE infusion dose reaches 0.3 µg kg^{-1} min^{-1}. Once the NE dose exceeds this threshold, the anaesthesiologist may initiate a third-line vasopressor infusion (typically vasopressin). The relatively high threshold of NE recommended before adding a third-line vasopressor was chosen to maximise the observable effect of the study drug on the primary outcome. If the third-line drug is not effective in maintaining a MAP ≥65 mm Hg, a fourth-line vasopressor infusion may also be initiated (typically epinephrine). If at any time the anaesthesiologist decides an additional vasopressor or inotrope is clinically required, for example in the case of bradycardia or myocardial dysfunction, the protocol can be overridden and the third- or fourth-line drug initiated even if the NE infusion dose is <0.3 µg kg^{-1} min^{-1}. Usage of third- and fourth-line vasopressors and the reason for initiation are recorded on the case report form. The anaesthesiologist may use their discretion to make other deviations to the vasopressor management protocol in the best interest of clinical care.

The study drug is discontinued before the end of the procedure. When the surgeon begins to close the abdomen at the end of LT, the anaesthesiologist begins to decrease the study drug dose rapidly until it is discontinued. If necessary, the NE infusion dose is increased as needed to maintain a MAP ≥65 mm Hg. In this trial, the study drug infusion is not continued in the intensive care unit after LT.

Box 2 Primary and secondary endpoints.

Primary Endpoint
Total dose of norepinephrine (NE), averaged over case duration and total body weight, used during LT to maintain a MAP ≥65 mm Hg.
Secondary Endpoints
Third- and fourth-line vasopressors
Vasopressin
⇒ Proportion of subjects requiring vasopressin infusion during LT
⇒ Dose of vasopressin (units or NE equivalents) administered during LT
⇒ Duration of vasopressin infusion (minutes)
Epinephrine
⇒ Proportion of subjects requiring epinephrine infusion during LT
⇒ Dose of epinephrine (µg or NE equivalents) administered during LT, excluding boluses within the 5 minutes immediately following portal reperfusion
⇒ Duration of epinephrine infusion (minutes)
Haemodynamics and biomarkers
⇒ Duration (minutes) with MAP <65 mm Hg
⇒ Change in direct renin (pg mL^{-1}), from the start of surgery until 2 hours after portal reperfusion
Clinical outcomes
⇒ Incidence of severe (stage 2 or 3) acute kidney injury within 48 hours after LT
⇒ Major adverse kidney events at 30 days after LT
⇒ Incidence of early allograft dysfunction
⇒ Model for early allograft function score
⇒ Duration of renal replacement therapy after LT
⇒ Duration of intensive care unit stay after LT
⇒ Duration of hospital stay after LT
⇒ Subject and graft survival at 30 days after LT
⇒ Subject and graft survival at 1 year after LT
NE, norepinephrine; LT, liver transplantation; MAP, mean arterial pressure.

Box 3 Safety assessments and predefined adverse events.

Safety assessments
Methylene blue or hydroxocobalamin administered during LT for vasoplegia
Vasopressor infusion required at the time of leaving the operating room (after study drug discontinuation)
Name and dose (in native units and norepinephrine equivalents) of vasopressor required at the time of leaving the operating room (after study drug discontinuation)
Adverse events during administration of study drug
Severe hypertension (systolic blood pressure >180 mm Hg for >5 min)
Cardiac arrhythmias, requiring treatment (excludes bradycardia typically seen with portal vein reperfusion)
Bronchospasm, requiring treatment
Congestive heart failure, cardiogenic shock or cardiogenic pulmonary oedema
Adverse events within 48 hours of the end of liver transplantation
Thromboembolism (venous or arterial)
⇒ Includes venous thromboembolism, portal vein thrombosis, inferior vena cava thrombosis, catheter-associated thrombosis or superficial thrombophlebitis
⇒ Includes myocardial infarction, ischaemic stroke, transient ischaemic attack, peripheral arterial thrombosis or hepatic artery thrombosis
⇒ Excludes disseminated intravascular coagulation because features of this condition (thrombocytopenia, low fibrinogen and elevated prothrombin time) are highly prevalent during and after LT (liver transplantation)

Primary endpoint and sample size calculation

The primary endpoint is the total dose of NE, averaged over case duration and total body weight, used during LT to maintain a MAP ≥65 mm Hg (box 2). Preliminary data from our centre indicate that patients undergoing LT with MELD-Na Score ≥25 have higher vasopressor requirements (median NE equivalent dosage 0.11, Q1-Q3 0.05–0.18 µg kg^{-1} min^{-1}) during LT than those with scores <25 (median 0.05, Q1-Q3 0.02–0.10 µg kg^{-1} min^{-1}). To attain 80% power to detect a 50% reduction in NE dose by AngII infusion as compared with placebo at α=0.05 (one-tailed), an estimated sample size of 44 total subjects (22 in each treatment arm) is required. The target enrolment is 50 subjects to account for drop-out.

Outcomes and statistical analysis

For the primary endpoint, all eligible subjects who are randomised and receive the study drug are included in the intention-to-treat analysis. Subjects that complete the study without protocol violation are included in the per-protocol analysis.

Doses of NE administered by bolus or infusion are summed and the total NE dose is divided by total body weight and case duration, expressed as µg kg^{-1} min^{-1}. The case duration is defined as the start of surgery (skin incision) until the end of surgery (abdominal closure) and does not include time for anaesthesia induction, line placement or patient transport. Norepinephrine dose in each arm is summarised as median and IQR. The total dose of NE is compared between the two arms by a Mann-Whitney U test and significance declared if p<0.05 (one-tailed). A one-tailed test is justified given that assignment to AngII (a vasopressor drug) cannot plausibly increase the required NE dose.

The secondary endpoints for the trial are summarised in box 2.[22–26] Vasopressors are reported as raw doses or norepinephrine equivalent dosage.[13] Categorical variables are summarised by frequency and percentage and continuous variables as median and IQR by arm. Categorical variables are compared between the two arms by either chi-square or Fisher's exact test as appropriate. Continuous variables are compared between the two arms by two-sample t-tests or Mann-Whitney U tests if the normality assumption does not hold. Time-to-event data is described by the Kaplan-Meier method and compared between the arms by log-rank tests. All statistical analyses are performed in Stata, GraphPad Prism and R software.

Adverse events within 28 days of LT are tabulated by treatment group and include the number of subjects that experienced the event, the rate of occurrence, severity and relationship to study drug (box 3). Serious adverse events are reviewed by an independent Data and Safety

	STUDY PERIOD						
	Enrollment	Allocation		Post-allocation			Close-out
	In hospital	In operating room		Post-surgery			Post-discharge
TIMEPOINT	Before entering operating room	Before surgical incision	NE dose > 0.05 µg kg^{-1} min^{-1}	Within 48 h	28 days	1 year	1 year (phone call)
ENROLLMENT: Eligibility screen	X						
Informed consent	X						
Randomization		X					
INTERVENTION: AngII Infusion			● — ●				
Placebo infusion			● — ●				
ASSESSMENT: Demographics	X						
Medical History	X			X	X	X	X
Physical Exam	X			X	X	X	
Concomitant Medication Review	X						
Routine Labs and Studies	X	X	X	X	X	X	
Blood and Urine Collection		X	X				
ADVERSE EVENTS: Severe Hypertension			X				
Thromboembolism				X			
Other			X	X	X		

Figure 2 Study schedule of enrolment, interventions and assessments. AngII, angiotensin II; NE, norepinephrine.

Monitoring Board that may make recommendations to adjust the trial protocol. Predefined safety outcomes are also collected for descriptive purposes (box 3). Given the incidence of early thromboembolism after LT is less than 10%,[27] this trial lacks the power to detect a true difference in this complication and data will be purely descriptive.

Recruitment and consent

The schedule of study procedures is shown in the SPIRIT figure (figure 2). Subjects are recruited from a high-volume liver transplant centre (average of 160 deceased donor transplants annually, 2021–2023). Enrolment began in May 2021 and is ongoing. Written consent (online supplemental file 1) is obtained by a physician along with trained study personnel. The information is presented orally and in written form in the subject's primary language. Consent forms are available in English, Spanish and Chinese. If the subject lacks capacity to provide consent, written consent is obtained from a legally authorised representative. When possible, subjects consented through a legally authorised representative are re-consented for use of data and specimens for research after regaining capacity.

Randomisation and blinding

At the time of entry into the operating room for LT, subjects are randomised to the experimental treatment (AngII infusion) or placebo (0.9% saline infusion) in a 1:1 ratio using a stratified block randomisation scheme with block size of four. The randomisation is stratified according to the presence or absence of preoperative RRT immediately prior to LT and the use of normothermic machine perfusion of the liver graft. The randomisation scheme is maintained by Randomize.net and accessed through a secure web portal.

After randomisation, the group assignment is visible only to the research pharmacist. Investigators, research staff, subjects and clinicians (anaesthesiologists, surgeons and nurses) are blinded to the study drug assignment. Infusion bags are prepared by pharmacy staff with identical packaging and labelling for either AngII or saline placebo. The bags are then transported directly to the

anaesthesia team in the operating room for administration. Drug infusion pumps are identically programmed as angiotensin II, 2.5 mg in 500 mL (5000 ng mL^{-1}), using the subject's total body weight, units of ng kg^{-1} min^{-1}, regardless of the actual study drug assignment.

During clinical care, anaesthesiologists may sometimes be able to identify the study drug based on the subject's blood pressure response to the infusion. To quantify inadvertent unblinding, the attending anaesthesiologist is asked to record their best guess of the study drug identity (AngII or saline placebo) on the case report form at the end of each case.

Data collection

Preoperative variables including subject demographics, medical history, medications, laboratory values and vital signs are extracted from the electronic medical record (EMR) and recorded in a secure REDCap database. Intraoperative variables including operative and ischaemia times, caval clamping technique, fluid totals, transfusions, arterial blood gases and laboratory values (haemograms and coagulation tests) are also recorded. Haemodynamics are automatically recorded every 1 min in the EMR. Drug doses, infusion titrations and fluid administrations are recorded in real time by the anaesthesiologist. Paper source documents identified by the study identification code are maintained to record all observations and other pertinent data for each subject. No protected health information is recorded on the source documents.

Biospecimen collection

Research involving human specimens is carried out in accordance with all relevant guidelines and regulations. Blood is collected from the subject's arterial line and urine from the bladder catheter at two timepoints, baseline (surgical incision) and 2 hours after portal vein reperfusion. Study personnel prepare ethylenediaminetetraacetic acid plasma and serum samples by centrifugation. Samples are frozen for biomarker analysis. Direct renin concentration is measured by enzyme-linked immunosorbent assays (DRG, International, Inc., Springfield, NJ, USA).[14] The change in direct renin between time points is calculated as a biomarker of the neurohormonal response to study drug.

Withdrawals and protocol deviations

Subjects who wish to withdraw from the trial have their data excluded from analysis. While rare, if the threshold dose of NE required for study drug initiation (0.05 µg kg^{-1} min^{-1}) is not met during LT, the subject is withdrawn before entering the trial and is not included in the intention-to-treat analysis. Protocol deviations such as early discontinuation of the study drug or failure to follow the titration protocol are recorded. Subjects experiencing a protocol deviation are included in the intention-to-treat analysis but excluded from the per-protocol analysis. Adverse events are documented and followed until resolution.

Patient and public involvement

A community member was part of the Institutional Review Board committee that reviewed and approved the study protocol. Otherwise, there is no patient or public involvement.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

The study protocol was approved by the University of California, San Francisco Institutional Review Board (#20–30948). A waiver of Health Insurance Portability and Accountability Act authorisation was granted for purposes of screening and recruitment. Written informed consent is obtained from all subjects as described under *Recruitment and Consent*. The consent form includes specific permission for use of human specimens (blood and urine) for research.

Experiments involving human specimens

Biomarker measurements on human blood and urine specimens are conducted in accordance with all relevant guidelines and regulations. These experiments were approved by the University of California, San Francisco Institutional Review Board and the Institutional Biosafety Committee (#BU175175).

Dissemination plans

This protocol was presented in oral format at the Society for the Advancement of Transplant Anesthesia spring 2023 meeting and in poster format at the International Anesthesia Research Society 2023 meeting. On completion of enrolment and data analysis, the results will be submitted for written publication to a peer-reviewed journal focused on anaesthesiology or transplantation research.

Acknowledgements The authors acknowledge mentorship and guidance from Dr Claus Niemann in designing the trial, and valuable feedback on the manuscript from Liam St. Hilaire.

Contributors MB obtained funding for the trial and oversees the project. MB, ELB, DA, RK and ML designed the trial. MB and ATT wrote the manuscript. MR helped revise the manuscript. SGM assists with data collection. ATT, MR and ES assist with patient consent and data collection and entry. GRR provided surgical advice and helped develop exclusion criteria. MP helped design the titration protocol. SF oversees research pharmacy procedures.

Funding This work was supported by the University of California, San Francisco Liver Center grant number NIH P30 DK026743.

Competing interests MB discloses that support was provided by La Jolla Pharmaceutical Company (now Innoviva, Waltham, MA, USA) for this trial as part of an investigator-initiated research proposal. This support consisted of study drug (AngII) at no cost for trial patients only, and $14 231 USD (direct plus indirect costs) to support an assistant research coordinator. La Jolla Pharmaceutical Company reviewed the protocol before trial initiation but suggested no changes. The authors have sole responsibility (independent of La Jolla Pharmaceutical/Innoviva) for conduct of the trial, analysis and interpretation of data, assignment of adverse events and dissemination of results. ML has received consulting fees from La Jolla Pharmaceutical Company, Alexion Pharmaceuticals and SphingoTec GmbH. All other authors have no competing interests to disclose.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods and analysis section for further details.

Patient consent for publication No individual data is reported.

Provenance and peer review Not commissioned; externally peer reviewed.

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