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Protocol

Functional echocardiography for management of shock in neonates - study protocol for a randomized controlled trial

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ABSTRACT

Background: Shock is common in sick neonates and is associated with a high mortality. Detection and management of shock by monitoring clinical parameters may be inadequate due to inconsistent association with tissue perfusion. We hypothesize that objective assessments of cardiac functions may help to match the pathophysiology of shock with the pharmacological action of a vasoactive drug. This may lead to earlier resolution of shock and reduced incidence of mortality or brain injury. To test this hypothesis, this study aims to evaluate the efficacy of adding functional echocardiography to standard clinical assessment in improving short-term outcome of neonates with clinical features of shock.
Methods: This study will be an open-labeled randomized controlled trial, conducted in all inborn neonates born at >27 weeks of gestation who develop clinical signs of shock. Enrolled neonates will be randomized into two groups: the echo group and the control group. Neonates in the echo group will be assessed for management of shock by both standard clinical evaluation and functional echocardiography. Neonates in the control group will be assessed for the management of shock by standard clinical evaluation. Primary outcome will be survival without requirement of inotropic support at 72 hours of randomization. Secondary outcomes include time to hemodynamic stability, duration of inotropic support and incidence of abnormal cranial ultrasound.
Conclusions: The trial intends to deduce the advantages, if any, of addition of functional echocardiography to standard clinical assessment to guide management of shock among preterm and term neonates.
Trial registration: CTRI number: CTRI/2023/08/056672.

Keywords: Echocardiography, Shock, Blood pressure, Neonate

INTRODUCTION

Shock is a state of cellular energy failure resulting from various pathogenetic mechanisms including myocardial dysfunction, hypovolemia, and vasoregulatory failure.[1] Although the true incidence of shock in small and sick neonates is unknown, about 50% of very low birth weight (VLBW) neonates admitted to the neonatal intensive care unit (NICU) develop 'low' blood pressure or hypotension at some point of time.[2] Immaturity of the cardiovascular system coupled together with impaired compensatory mechanisms predisposes neonates, especially preterm infants to end-organ injury related to hypoperfusion and hypoxemia.[3] Hypotension is associated with an increased risk of intraventricular hemorrhage (IVH), neuro-developmental disabilities, and death.[4]

Various clinical and bedside laboratory parameters including heart rate, capillary refill time (CRT), blood pressure, acid-base status and urine output have

traditionally been used to define shock. Many of these signs have low sensitivity and appear only when shock has entered uncompensated stage.[5] Despite being in common use for both diagnosis and management of shock, there is very limited data validating the accuracy of clinical signs for detecting low systemic blood flow, especially in preterm infants.[6] Although blood pressure remains the most commonly monitored circulatory marker, its association with systemic blood flow is variable.[7] Due to limited potential of clinical signs in early identification of shock, there is a need for other potential tools that could facilitate timely detection of circulatory compromise. Functional echocardiography is one of the emerging technologies that can be used to measure cardiac function in critically ill neonates.[8] Functional echocardiography can provide an objective evaluation of cardiac function and output, identify a hemodynamically significant patent ductus arteriosus (PDA) and allow evaluation of therapeutic interventions.[9] Functional echocardiography offers advantages including the provision of real-time information on circulatory function, rapidity of data acquisition, and allowing serial functional assessments.[10] Clinical signs including CRT, mean blood pressure and systolic blood pressure have been shown to be correlated with the blood flow in the superior vena cava (SVC).[6] Collapsibility of inferior vena cava (IVC) during breathing movements has shown a good correlation with central venous pressure measurement.[11] SVC flow, in combination with CRT has been found to be a predictive marker of adverse outcome in neonatal shock.[12] Although echocardiography has been used in the assessment of hemodynamic variables in various studies, these studies have not utilized echocardiographic assessment for management of shock.[6,12-15]

Using functional echocardiographic assessment of hemodynamics including circulatory volume, cardiac contractility, cardiac output, and systemic blood flow, one can gather valuable information that can guide in diagnosis, categorization, and management in neonatal shock. The study aims to evaluate if, among neonates with shock, the addition of functional echocardiography to clinical evaluation is associated with faster resolution of shock. The primary objective of the study is to evaluate the efficacy of adding functional echocardiography to standard clinical assessment in improving survival without need for inotropic support in neonates with shock. The secondary objectives include the efficacy of adding functional echocardiography to standard clinical assessment for the management of shock on time to reach hemodynamic stability, total duration of shock, and the incidence of abnormal cranial ultrasound.

METHODS

Study design and setting

This will be an open-labeled randomized controlled trial conducted in the neonatal intensive care unit of a tertiary care teaching hospital in India. The study will be conducted over a period of 18 months from October 2023 to March 2025.

The study has been approved by the Institutional Ethics Committee and is registered prospectively in the Clinical Trial Registry of India (CTRI/2023/08/056672). The study protocol will be reported in accordance with the consolidated standards of reporting trials (CONSORT) statement.

Study subjects

Inclusion criteria

All inborn neonates born at ≥28 completed weeks of gestation and who develop clinical signs of shock will be eligible for inclusion in the study.

The shock will be defined as the presence of at least two of the following seven criteria: heart rate >180 per minute, low blood pressure (systolic, diastolic, or mean blood pressure <5th percentile for gestation or mean blood pressure <30 mm of Hg), CRT >3 seconds, perfusion index (PI) <0.44, central-to-peripheral temperature difference (TD_{cp}) >2 °C, oliguria (<0.5 ml/kg/hour) during the preceding 6 hours, and metabolic acidosis (base excess < -5 or lactate >5 mMol/l).[15-22]

Exclusion criteria

Neonates with any of the following will be excluded from the study: major congenital malformations, being treated for persistent pulmonary hypertension of newborn (PPHN), and moribund status.

Randomization and allocation concealment

Using a web-based random sequence generator (www.sealedenvelope.com), a co-investigator not involved in the recruitment of subjects will generate a random number sequence of variably sized permuted blocks. The randomization will be stratified for gestation at birth: 28-34 weeks and >34 weeks. The sequence will be kept in serially-numbered sealed opaque envelopes bearing slips of paper with the allocated intervention. Multiple births will be randomized separately. Randomization will be done within 30 minutes of the detection of clinical signs of shock.

Blinding

Due to the nature of the intervention, the clinical care team will not be blinded to the study group allocation.

Study flow

Assessment of the eligibility for the study will start immediately once a neonate shows signs of hemodynamic instability. Management of hemodynamic instability will start with administration of a saline bolus if not

contraindicated clinically. Neonates who are eligible as per the inclusion and exclusion criteria defined above will be enrolled after obtaining parental consent. Enrolled neonates will be randomized to one of the two study groups: the echo group and the control group. Neonates in the echo group will be assessed for management of shock by both standard clinical evaluation and functional echocardiography. Neonates in the control group will be assessed for the management of shock by standard clinical evaluation (Figure 1).

Clinical evaluation

Once the patient is enrolled**,** baseline hemodynamic variables including heart rate, CRT, blood pressure, PI, TD_{cp}, respiratory status, and oxygen saturation will be recorded. Systolic, diastolic, and mean arterial pressures will be recorded either non-invasively by oscillometric method or from an intra-arterial catheter. TD_{cp} will be measured with two separate temperature probes fixed at the right hypochondrium and sole of one of the feet for central and peripheral temperatures respectively. CRT will be measured on the sternum by applying pressure using the soft pad of an index finger for 5 seconds to blanch the area and then releasing the finger to note the return of circulation with the help of a digital timer. Oxygen saturation and PI will be measured by attaching a pulse oximeter probe to the right upper limb.

Functional echocardiography

Guidelines used for obtaining echocardiographic images will be in accordance with international evidence-based guidelines on point-of-care ultrasound (POCUS) for critically ill neonates and children issued by the POCUS working group of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC).[23] All echocardiographic parameters will be noted by the principal investigator as per protocol on MyLabX7 (Esaote) using high-frequency phased-array probe.

Neonates enrolled in the Echo group will be assessed for the following four parameters: preload, volume status, and fluid responsiveness, left ventricular function, cardiac output, and presence of PDA.

Preload, volume status, and fluid responsiveness

Qualitative assessment will be done by eyeballing the heart and the inferior vena cava (IVC) for underfilling in spontaneously breathing neonates. Signs of fluid deficit include 'kissing ventricles' on the apical four-chamber view, narrow IVC lumen, and IVC collapsibility on the subcostal view. Quantitative assessment will be done by measuring the IVC collapsibility index on subcostal view.[24] IVC collapsibility index is calculated by measuring the maximum (D_{max}) and minimum IVC diameter (D_{min}) from the subcostal view on echocardiography.

$$IVC\ collapsibility\ index = \frac{D\ max - D\ min}{Dmax} \times 100$$

IVC collapsibility index of >55% will be considered as predictive of fluid responsiveness.[25]

In mechanically ventilated patients IVC distensibility index will be used by measuring the D_{max} and D_{min} of IVC from the subcostal view.

$$IVC\ distensibility\ index = \frac{D\ max - D\ min}{Dmin} \times 100$$

IVC distensibility index of >18% will be considered as predictive of fluid responsiveness.[25]

Left ventricular function

Qualitative assessment of the left ventricular contractility will be done by eyeballing from different echocardiographic views. The quantitative assessment of left ventricular function will be done by measuring fractional shortening (FS) using the parasternal long-axis view in M-mode and will be calculated using the following formula.

$$Fractional\ shortening = \frac{Left\ ventricular\ end{-}diastolic\ diameter - Left\ ventricular\ end{-}systolic\ diameter}{Left\ ventricular\ end{-}diastolic\ diameter} \times 100$$

Normal fractional shortening will be taken as 26-46%.[25]

Cardiac output

Ventricular output will be measured by using the following formula.

$$Left\ ventricular\ output\ (ml/kg/min) = \frac{Heart\ rate \times Cross{-}sectional\ area\ of\ aortic\ valve\ annulus \times Velocity{-}time\ integral}{Body\ weight\ (kg)}$$

The cross-sectional area (CSA) will be calculated by measuring the diameter at the hinge point of the aortic valve annulus at the end-systole in the parasternal long-axis view. The velocity-time integral (VTI) will be measured just proximal to the aortic valve by using pulse-wave Doppler in the apical five-chamber view. The normal ventricular output will be taken as 150–300 ml/kg/min.[26]

Presence of PDA

The presence of PDA is assessed in the modified parasternal short-axis view. The following characteristics will be noted: diameter, flow direction, and the ratio of systolic and diastolic flow velocities. Pulmonary overcirculation will be assessed by measuring the left atrial-aortic root ratio (LA: Ao ratio). A diagnosis of hemodynamically significant PDA will be made when the duct diameter is ≥1.5 mm or LA: Ao ratio is ≥1.5.[27]

Intervention

Echo group

The first assessment by functional echocardiography will be done immediately after the neonate has received a saline bolus which will be the first line of treatment in both study groups. A repeat assessment will be done after starting the treatment based on the first assessment once the patient has been hemodynamically stable for two hours without requirement of further change of inotropic support. A third assessment, if required, will be done in those circumstances where shock is refractory to two inotropic agents. After each assessment, the shock will be managed as per the following protocol given in Figure 2.

If there are signs of hypovolemia, normal saline 10 ml/kg over 10-30 minutes will be given and will be repeated for persistent hypovolemia. Dobutamine will be started for fluid-resistant shock.

If the decreased left ventricular output is due to poor contractility, dobutamine will be started at 10 µg/kg/min. The dose will be increased by 5 µg/kg/min every 15-20 mins to a maximum of 20 µg/kg/min. Epinephrine will be given if shock does not respond to the above treatment at a dose of 0.1 µg/kg/min and increased every 10-15 minutes to a maximum of 0.5 µg/kg/min.

For normal to increased LV output, if there is hemodynamically significant PDA with left-to-right shunt, first-line treatment will be shunt limitation strategies including restricted fluid input, permissible hypercapnia (PCO_2 50–60 mmHg), optimization of FiO_2, PEEP, and hemoglobin, and medical ductal closure using paracetamol or ibuprofen. The second line of treatment will be dobutamine. If there is no PDA, dopamine will start. If shock is unresponsive to the maximum dose of dopamine, vasopressin or Noradrenaline will be added. Hydrocortisone (1 mg/kg/day q 6 hours) will be added once the baby is on two inotropes. Milrinone will be added if cardiac contractility remains poor at this stage.

In case all the echocardiographic parameters are normal, management will be as per clinical evaluation.

Control group

Management of shock will be guided by clinical evaluation (Figure 3).

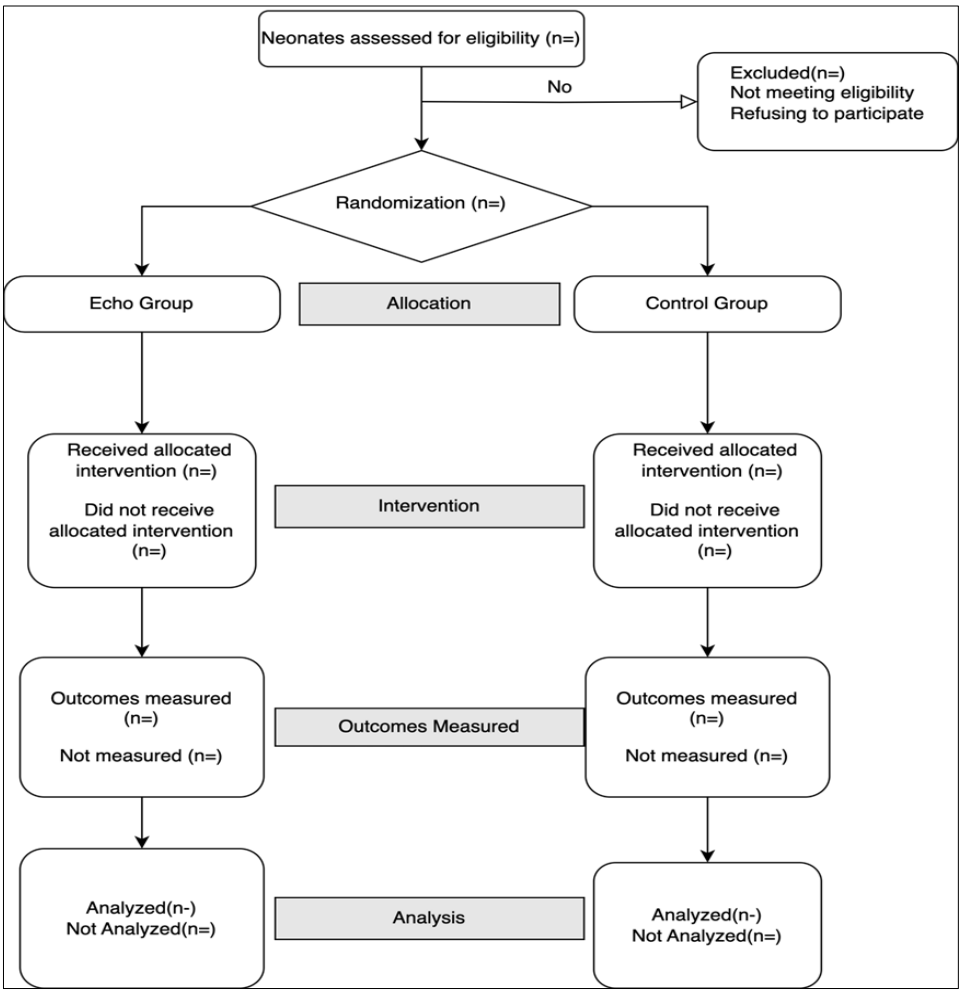

Figure 1: Trial flow.

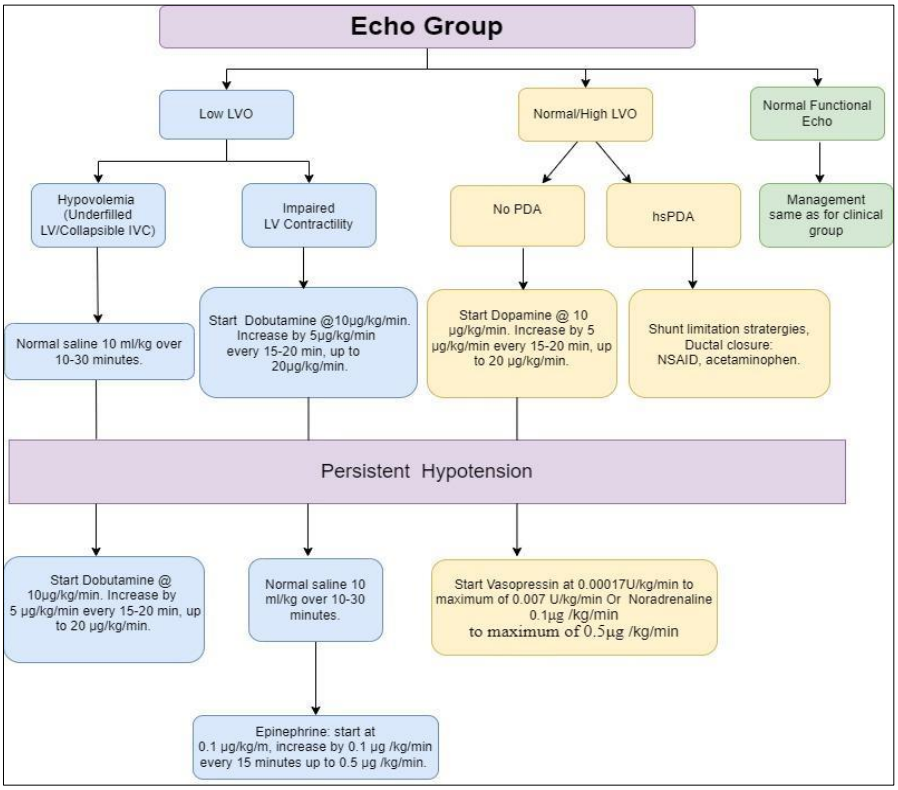

Figure 2: Management of shock in echo group.

Hydrocortisone at 1 mg/kg/dose 4-6 hourly will be considered once baby is on two inotropes. Therapeutic endpoints include a normalization of clinical parameters used to define shock and include CRT of <3 seconds, PI of >0.44, urine output greater than 1 ml/kg/hour, central to peripheral temperature difference of <2 ^{0}C and normalization of blood pressure

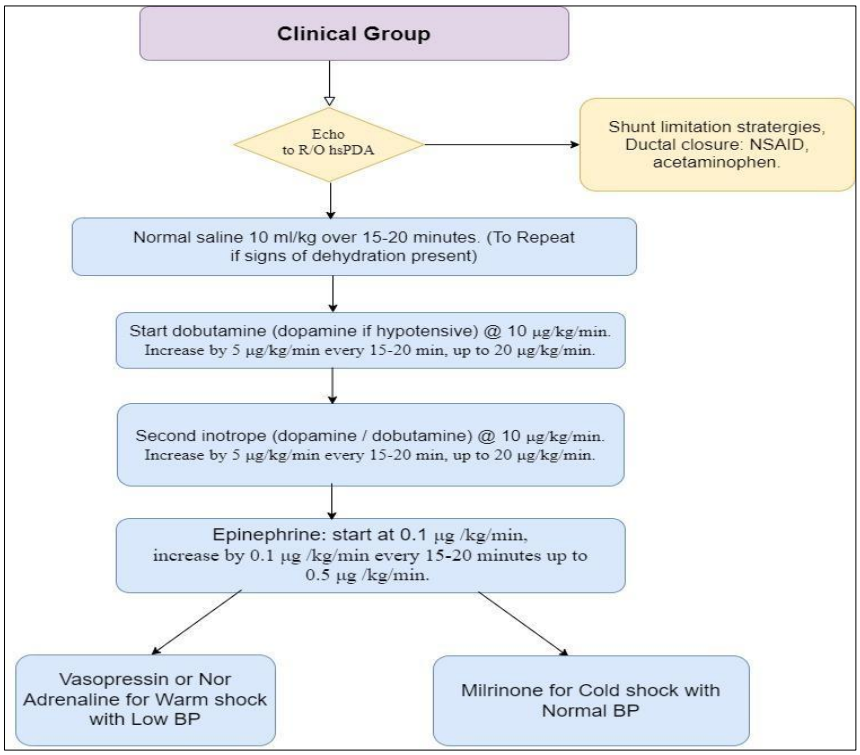

Figure 3: Management of shock in control group.

Hydrocortisone at 1 mg/kg/dose 4-6 hourly will be considered once baby is on two inotropes. Therapeutic endpoints include a normalization of clinical parameters used to define shock and include CRT of <3 seconds, PI of >0.44, urine output greater than 1 ml/kg/hour, central to peripheral temperature difference of <2 ^{0}C and normalization of blood pressure

If suspected (based on clinical assessment and gestation), a physician not involved in the study will do an echocardiography for ruling out PDA. No other echocardiographic parameter will be assessed.

A second saline bolus will be given if there are signs of hypovolemia and no PDA is suspected or present.

Neonates who do not respond to Fluid therapy will be labeled as having fluid refractory shock and will be started on inotropes.

If BP is normal, dobutamine will be started as the first inotrope at 10 µg/kg/min and if needed, increased by 5 µg/kg/min every 15-20 mins to a maximum of 20 µg/kg/min. If BP is low, dopamine at the same dose increases by 5 µg/kg/min every 15-20 mins to a maximum of 20 µg/kg/min for persistence of shock.

Dopamine will be the second inotrope (dobutamine in case the first inotrope was dopamine) and will be escalated as above. Hydrocortisone at 1 mg/kg/dose 6 hours will be added once the baby is on two inotropes.

For persistent shock, 0.1 µg/kg/min of epinephrine will be started as the third line inotropes and if required, will be increased every 10-15 minutes to a maximum of 0.5 µg/kg/min. Dopamine will be tapered once epinephrine is started.

Vasopressin or noradrenaline will be added for the warm shock with low blood pressure and milrinone will be started for the cold shock with normal blood pressure.

Therapeutic endpoints (common to both the study groups)

Normalization of clinical parameters used to define shock and include CRT of <3 seconds, PI of >0.44, urine output greater than 1 ml/kg/hr, TD_{cp} <2 °C, and blood pressure >50th centile. If at any time, blood pressure is >95th percentile for gestational age, inotropes will be tapered. Once cardiovascular therapeutic endpoints are achieved, the drugs will be tapered every 6 hours, in steps of 5 µg/kg/min for dopamine and dobutamine and 0.1 µg/kg/min for epinephrine and norepinephrine.

Supportive care

Neonates in both the study groups will receive standard care as per the unit protocol.

Study outcomes

Primary outcome

Survival without inotropic support at 72 hours of randomization.

Secondary outcomes

Time to hemodynamic stability - defined as the time from randomization to normalization of parameters used to define shock and no further requirement of inotropic support for the next 120 minutes; survival till discharge; and incidence of abnormal cranial USG (severe intraventricular hemorrhage or cystic periventricular leukomalacia) at discharge.

Other outcomes

Total duration of inotropic support; time to complete the resolution of shock; and maximum vasoactive inotropic score (VIS) calculated as following formula.

$$VIS = Dobutamine\ (\mu g/kg/min) + dopamine\ (\mu g/kg/min) + epinephrine\ (\mu g/kg/min) \times 100 + norepinephrine\ (\mu g/kg/min) \times 100 + milrinone\ (\mu g/kg/min) \times 10 + vasopressin\ (\mu g/kg/min) \times 10000$$

Sample size

The primary outcome of the study is the survival without the need for inotropic support at 72 hours after randomization. We reviewed the data of our inborn neonates for the year 2022 which showed that out of 91 neonates who developed shock, 57% survived till discharge. To improve the survival of neonates with shock from 57% to 87%, a total of 41 neonates will need to be recruited in each arm of the study.

Statistical analysis

Study data will be collected using a specially designed and pre-tested proforma. Data will be entered into a spreadsheet. Continuous variables will be expressed as mean and standard deviation if normally distributed and as median and interquartile range if non-normally distributed. Categorical variables will be expressed as numbers and proportions. Quantitative data with normal distribution will be compared using the student t-test and those with skewed distribution will be analyzed using the Mann-Whitney U test. Categorical data will be compared using Chi-square or Fisher exact test as applicable. P value of <0.05 will be considered significant. Time to event will be analyzed using the Kaplan-Meier survival analysis. If baseline variables are unequally distributed, the treatment effect will be adjusted by conducting a logistic regression. The analysis will be by intention-to-treat principle.

RESULTS

Baseline characteristics will be presented in the two groups as outlined in Table 1.

Primary outcome will be survival without requirement of inotropic support at 72 hours of randomization. Secondary outcomes to be assessed are time to hemodynamic stability, total duration of inotropic support, incidence of abnormal cranial ultrasound at discharge and other outcomes as presented in Table 2.

Table 1: Baseline neonatal characteristics.

Baseline variables	Echo group	Control group
Gestation age (weeks+days)/birth weight (grams)		
Gender (male/female/ambiguous)		
Apgar scores (1 min and 5 minute)		
Antenatal steroids (Y/N)		
Clinical chorioamnionitis (Y/N)		
Intrapartum antibiotics (Y/N)		
$MgSO_4$ (Y/N)		
Significant fetomaternal hemorrhage (Y/N)		
Perinatal asphyxia (Y/N)		
Delivery room CPAP (Y/N)		
Surfactant (Y/N)		
Caffeine treatment (Y/N)		
Antibiotics (Y/N)		
Clinical characteristics		
Heart rate		
BP (SBP/DBP/MBP)		
CRT		
Urine output		
PI<0.44		
cpTD		
Metabolic acidosis (lactate/base excess)		
Echo parameters		
LVO (ml/kg/min)		
Eyeballing		
Collapsible IVC (Y/N)		
IVC-CI or IVC-DI		
Eyeballing		
Poor LV contractility (Y/N)		
Left ventricle FS		
hsPDA		
Normal functional echo (Y/N)		

Table 2: Neonatal outcomes.

Outcomes	Echo group	Control group
Inotrope requirement at 72 hours (Y/N)		
Time to hemodynamic stability (hours)		
Hemodynamically significant PDA(Y/N)		
Duration of inotropic support (hours)		
Clinical parameters (after hemodynamic stabilisation)		
Heart rate		
Blood pressure (SBP/DBP/MBP)		
PH/lactate/base excess/bicarbonate		
Echo parameters (after hemodynamic stabilization)		
Normalization of parameters (Y/N) LVO (ml/kg/min)		
IVC-CI/IVC-DI		
LV FS		
Maximum vasoactive inotropic score (VIS)		
Time to resolution of shock (hours)		

Continued.

Outcomes	Echo group	Control group
Duration of assisted ventilation (days)		
Total duration of antibiotic treatment (days)		
Incidence of abnormal cranial USG		
Time to reach full enteral feeds (days)		
Necrotizing enterocolitis (as per Bell's staging)		
Bronchopulmonary dysplasia		
Duration of NICU stay (days)		
Retinopathy of prematurity (Y/N)		

DISCUSSION

The proposed study will compare the outcomes of management of shock that has been assessed either clinically only or by both clinical and echocardiographic parameters. Clinically, shock will be assessed by variables which include heart rate, blood pressure, capillary refill time, central to peripheral temperature difference, perfusion index, urine output and metabolic acidosis. Based on these parameters and with the background of underlying clinical condition, etiology of shock will be determined and inotropes will be started accordingly. Functional echocardiographic evaluation of neonates can include assessment of preload, left ventricular contractile function, cardiac output, systemic blood flow, and presence of PDA. By assessment of these echocardiographic parameters, we can recognize the hemodynamic derangements and possibly frame the etiological basis of shock. Once assessed, the inotrope with most appropriate physiological action will be started. Based on our study, we will be able to determine the possible benefits of adding functional echocardiography to the clinical assessment for management of shock in neonates.

Clinical and a variety of echocardiographic parameters have been evaluated across various studies in neonates with or without shock. The studies reporting the role of echocardiography in the management of shock can be divided into four categories.

At the outset are those studies that have evaluated the correlation between clinical signs of shock and parameters of functional echocardiography. Data from most of these studies shows that clinical signs correlate well with the echocardiographic parameters in neonates with shock. Osborn et al demonstrated that CRT of >3 seconds had 55% sensitivity and 81% specificity, a mean blood pressure of <30 mm Hg had 59% sensitivity and 77% specificity, and a systolic blood pressure <40 mm Hg had 76% sensitivity and 68% specificity for detecting low SVC flow.[6] In 2017, Mugloo et al published data from a cross-sectional analytical study of 50 neonates and found a strong negative correlation between the IVC-collapsibility index and CVP (r= −0.968, p=0.000).[11] In a multicenter retrospective study, Kharrat et al reported data from 1060 echocardiographic examinations in 485 neonates that blood pressure parameters correlate poorly with LV output, irrespective of gestation and underlying etiology.[14] A positive correlation was seen between the SVC flow and PI (r=0.509, p<0.001) in a study conducted by Takahashi et al, who showed that the best cut-off value for the PI to detect low SVC flow is 0.44.[17]

The second category of studies include those evaluating the changes in functional echocardiographic parameters in neonates with shock. Gill et al from a prospective observational study conducted on 75 VLBW neonates reported that median shortening fraction and left ventricular contractility and output were significantly lower in the neonates with shock that in control subjects.[28] In 2014, Saini et al, from a prospective observational study of 104 preterm neonates enrolled into septic shock group (n=52) and healthy control group (n=52) reported significantly higher left ventricular (LV) output in neonates with septic shock than in controls (median [IQR]: 305 [204, 393] versus 233 ml/kg/min [204, 302]; p<0.001), but a similar ejection fraction in the two groups (55±12% versus 55±5%, p=0.54).[29] From a cross-sectional study comparing echocardiographic parameters of 30 term neonates with clinically detected shock and 30 hemodynamically stable neonates, Bandyopadhyay et al found that IVC collapsibility, fractional shortening, ejection fraction, cardiac output, and SVC flow were significantly lower whereas myocardial performance index (MPI) was significantly higher in babies with cardiogenic and septic shock as compared to the controls.[30]

The third category of studies are those that evaluate responses to different types of inotropic agents in neonates with shock. In 2009, Bravo et al conducted a randomized, controlled trial in 28 neonates randomized to receive either dobutamine or placebo and found that all randomized neonates except 2 achieved and maintained an SVC flow >41 ml/kg/min; however, neonates treated with dobutamine showed a higher heart rate and improved base excess compared with those treated with placebo.[31] Baske et al randomized 40 neonates with fluid-refractory septic shock into two groups to receive randomly allocated treatment with increasing doses of either dopamine or epinephrine.[16] The authors concluded that the proportion of neonates, who achieved reversal of shock (defined as systolic and diastolic BP >5th centile and CRT <3 s and left ventricular output ≥150 ml/kg/min) in the first 45 min (25 versus 30%; RR: 0.83, 95% CI 0.30, 2.29), hemodynamic stability (shock reversal for ≥120 min without escalation of vasoactive drugs) and mortality within first 28 days of life (70% versus 80%; RR 0.87, 95%

CI 0.61, 1.26) were comparable in the epinephrine and dopamine groups, respectively.

The fourth category of studies includes those investigating the role of functional echocardiography in the management of shock. There are no randomized controlled trials in this category. Objective assessments of cardiac functions may help to match the pathophysiology of shock with the pharmacological action of a vasoactive drug. This may lead to earlier resolution of shock and reduced incidence of mortality or brain injury. As no previous study has evaluated the role of functional echocardiographic in guiding the management of shock, this study has been planned to address the same.

CONCLUSION

The study will deduce any possible advantages of addition of functional echocardiography to routine practice of assessing tissue perfusion by clinical methods in the management of shock and compare the outcomes with assessment of shock by clinical parameters alone. Role of functional echocardiography as a non-invasive tool for accurate assessment of hemodynamic status in neonates and as guide in the categorization and monitoring of response to treatment in neonatal shock can therefore be elucidated.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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