

Oral Versus Intravenous Fluid Therapy for Hypernatremic Dehydration in Children Under Five with
Diarrhoea: A Randomized, Controlled, Non-Inferiority Trial
Research Protocol

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Project Summary

Principal Investigator: Dr Haimanti Saha	
Research Protocol Title: Oral Versus Intravenous Fluid Therapy for Hypernatremic Dehydration in Children Under Five with Diarrhoea: A Randomized, Controlled, Non-Inferiority Trial	
Start date: 1/13/2026	Estimated end date: 31/10/2027
Background (brief): a. Burden: Diarrhoeal disease remains one of the leading causes of death among children aged under five years. WHO recommends the use of appropriately prepared oral rehydration salt (ORS) solutions and supplemental zinc as the best remedy for most of the cases. At icddr,b Dhaka Hospital, we have noted an annual prevalence rate of 2.4-5.1% children with hypernatremia (defined as a serum sodium ≥ 150 mmol/L) mostly resulting from inappropriate preparation and use of ORS. Hypernatremic dehydration is a life-threatening condition, particularly in children under two years of age, with mortality rates reaching up to as high as 19%. Infants are highly susceptible due to immature renal function, increased insensible water loss, and limited ability to express thirst. Severe hypernatremia can cause cerebral complications such as brain shrinkage, haemorrhage, seizures, paralysis, and encephalopathy. Furthermore, rapid or improperly managed fluid and electrolyte treatment can increase the risk of cerebral oedema and death. b. Knowledge Gap: Although gradual sodium correction is widely recommended for hypernatremia, the optimal rate, route, and type of fluid therapy remain uncertain. Current treatment practices vary and no standardized protocol has been validated in randomized clinical trials for young children. This gap contributes to persistently high mortality and neurological morbidity. c. Relevance: This study is critical for improving management strategies for hypernatremic dehydration, especially in children under five, who are at high risk of developing hypernatremia. In low-resource settings like Bangladesh, where diarrhoea remains a major cause of child mortality, optimizing fluid therapy can significantly reduce deaths and complications. Findings will benefit icddr,b Dhaka Hospital and influence global treatment guidelines by promoting safer sodium correction to prevent cerebral oedema, seizures and other complications. Hypothesis: Oral fluid therapy, when administered using the same fluid volume and correction protocol as intravenous therapy, is not clinically inferior to intravenous fluid therapy in the management of hypernatremia in young children with diarrhea. Objectives: To compare the efficacy of two treatment arms-oral and intravenous, in the management of hypernatremic dehydration in children under five years of age with diarrhoea, focusing on mortality reduction. Methods: This will be a randomized, controlled, open-label, non-inferiority trial comparing intravenous (IV) versus oral rehydration therapy using standardized fluid volumes. A total of 268 children with serum sodium ≥ 150 mmol/L will be enrolled and randomized equally into two treatment arms. Both groups will receive the same calculated fluid volume based on standard paediatric protocols, administered either orally (ORS) or intravenously ($\frac{1}{2}$ strength acetate in 5% dextrose). Close monitoring of electrolytes, weight, and clinical signs will guide therapy. Outcome Measures: The primary outcome will be mortality from initiation of the intervention until hospital discharge. Secondary outcomes will include the rate of serum sodium decline, incidence of convulsions, and signs of fluid overload or renal impairment. Neurological outcomes will be assessed via the Glasgow Coma Scale (GCS) on admission and at discharge, and via the Denver Developmental Screening Test II (DDST-II) at 1- and 6-months post-discharge.	

Description of the Research Project

Hypothesis to be tested:

Does this research proposal involve testing of hypothesis: ☐ No ☒ Yes (describe below)

Primary Hypothesis: We hypothesize that oral fluid therapy, when administered using the same fluid volume and correction protocol as intravenous therapy, is not clinically inferior to intravenous fluid therapy in the management of hypernatremia in young children with diarrhea.

Scientific basis of the hypothesis: The hypothesis that oral fluid therapy is non-inferior to intravenous fluid therapy in managing hypernatremic dehydration in children is grounded in both physiological principles and clinical observations. Hypernatremia results from a deficit of free water relative to sodium, and its correction requires careful fluid replacement to restore plasma tonicity without inducing cerebral oedema. Currently IV therapy is the standard approach. Oral rehydration salt (ORS) solution, when properly administered, provides an effective balance of sodium and glucose that promotes intestinal sodium and water absorption, mimicking the natural mechanism of hydration. Clinical evidence, including studies from icddr,b, suggests that appropriately timed and dosed oral rehydration may be as effective as IV therapy in gradual sodium correction. It poses fewer risks of fluid overload, rapid sodium shifts, and nosocomial infections. Furthermore, ORS therapy avoids the technical complications associated with IV access in dehydrated children and is more feasible in resource-limited settings. Given these advantages and the lack of definitive evidence from randomized controlled trials, we plan this study.

Specific Objectives:

Primary objective:

To evaluate the non-inferior efficacy of oral fluid therapy with standard intravenous fluid therapy, in the management of hypernatremic dehydration in children under five years of age with diarrhoea, focusing on mortality till discharge.

Secondary objectives:

1. To quantify the rate of rapid reduction in serum sodium concentration (**>0.5mmol/L/hour or more than 12 mmol/L over any 24-hour period**) in each arm.
2. To identify the particular fluid therapy arm requiring ancillary interventions (e.g., 3% NaCl, anticonvulsants).
3. To track the frequency of abnormal weight gain ($\geq 5\%$ over any 12-hour period) in each arm.
4. To evaluate the events of renal impairment (acute kidney injury) between the study groups.
5. To identify predictors of poor neurological outcome at discharge, 1 month and 6 months of initiation of the treatment.
6. To compare the case fatality at 6-month follow-up between two treatment arms.

Background of the Project including Preliminary Observations:

Diarrhoeal disease remains one of the leading causes of death among children aged under five years of age. (1) The World Health Organization (WHO) recommends the use of appropriately prepared oral rehydration salt solution (ORS) and Zinc as the best remedy for diarrhoea.(2, 3) At icddr,b Dhaka Hospital, every year we found 2.4-5.1% children having hypernatremia, a serum sodium ≥ 150 mmol/L, mostly resulting from

inappropriate preparation and use of ORS. (4) In other hospital-based studies, the reported prevalence of hypernatremia in children with diarrhoea was 11.2% in Bangladesh (non-icddr,b), 7.2% in India, 14% in Iran, and 22% in Pakistan.(5-8) Hypernatremic dehydration is one of the most fatal types of dehydration, particularly in children under two years of age. Infants are at higher risk of developing hypernatremia due to immature renal function, increased insensible water loss, and limited ability to communicate thirst. Hypernatremia commonly occurs when there is excessive loss of water relative to sodium loss or disproportionate sodium intake compared to water intake.(9, 10)

The increase in plasma tonicity causes water movement across cell membranes, leading to intra-cellular dehydration. Brain cells are particularly vulnerable, and severe hypernatremia can induce brain shrinkage, potentially causing cerebral haemorrhage, seizures, paralysis, and encephalopathy. Rapid correction of hypernatremia is associated with the potential development of oedema and high fatality rates, necessitating a controlled reduction in serum sodium levels.(11)

Incorrectly prepared oral ORS solutions, including preparation errors and improper intake frequency, have been implicated in hypernatremia severity.(4, 12) Mortality rates in acute hypernatremia reach up to as high as 19%, with neurological complications occurring in 15% of cases.(4, 13) These include intellectual deficits, seizure disorders, and spastic paralysis. Seizures may result from hypernatremia itself or from overly rapid correction.(14)

Management Principles: Treatment of hypernatremia requires fluid administration to correct water deficits while limiting further water loss. Paediatric patients often present with concurrent hypovolemia due to gastrointestinal losses, requiring volume restoration with isotonic fluids before addressing hypernatremia. Ongoing monitoring of fluid status and frequent electrolyte assessments guide therapy adjustments.(15)

The goal of treatment is to restore plasma tonicity gradually. Rapid correction is recommended only in acute cases to prevent cellular dehydration effects. For hypernatremia developing over days, correction of serum sodium concentration should not exceed 0.5 mmol/L/h or 12 mmol/L/day, though no randomized trials specifically support this threshold.(16) The choice of replacement fluid depends on the type of fluid loss and concurrent electrolyte imbalances.(17)

Fluid Calculation Approaches:

Among the formulas used to estimate water deficit based on body weight and total body water (TBW), the Edelman equation and the Adroque and Madias equation, primary evaluated in adults, are the most commonly reported in the literature.

The Edelman equation for water deficiency is as follows:

$$\text{Water deficiency} = \text{TBW} \times [(\text{Serum sodium concentration}/140 - 1)]$$

This equation helps to estimate the amount of water needed to correct the serum sodium concentration back to 140 mEq/L. Here, the replacement fluid is calculated using a separate formula, making the process essentially a two-step procedure. The first step estimates the fluid deficit, while the second step calculates the amount of replacement fluid, which is then given over a period of 48 to 72 hours. The total amount of replacement fluid required based on the composition of the fluid being administered, particularly its sodium content.(18)

The Adrogue and Madias equation, which is derived from the Edelman equation, estimates the volume of fluid required for replacement in a single step. This formula is used to determine the amount of fluid to be administered over 24 hours to reduce serum sodium by 10 mEq/L.(15)

The Adrouge formula is widely accepted and commonly used by clinicians due to its simplicity in calculation. However, this formula has only been evaluated in adult populations. According to the Adrouge formula, the calculated fluid amount is administered over 24 hours, after which recalculation is performed based on the serum sodium level for the next 24- hour period. The volume of fluid required tends to increase as the sodium level decreases. This dynamic of fluid adjustment carries the potential for weight gain in children following the initial 24 hours of fluid therapy, especially since most of the rapid sodium reductions occur during this time, as reported in unpublished data.

The conventional Edelman is slower, with the amount of fluid administered during the first 24 hours being about two-thirds of the fluid calculated by the Adrouge formula. This rate remains consistent over the next 24-48 hours. In comparison, the Adrouge approach adjusts the fluid rate every 24 hours based on changes in serum sodium levels.(15, 16)Both the formula does not consider the current losses, which might change considerably over the treatment course. Both losses, including renal and extrarenal, need to be taken into consideration and also included in the overall fluid administration. Proper regulation in the fluid administration needs to be directed through frequent evaluation of the clinical status of the patient as well as serial monitoring of laboratory values within the treatment.

Paediatric textbooks such as *Nelson Textbook of Pediatrics* (21st edition) and *Ghai Essential Pediatrics* (9th edition) recommend managing hyponatremia by administering 1.25 to 1.5 times the maintenance fluid requirement over a period of 24 to 84 hours, depending on the severity of hyponatremia.(19, 20) The commonly recommended fluid for this purpose is 0.45% sodium chloride in 5% dextrose. This approach does not involve a direct calculation of fluid deficit using formal equations such as Edelman's. Instead, it assumes that the fluid deficit can be adequately addressed by providing a higher-than-maintenance fluid volume. The maintenance requirement can be calculated using standard Holliday Seger formula, that is 100 ml/kg/day for first 10 kg and 50ml/kg/day for next 10 kg (11-20kg) then for each kg over 20kg it will be 20ml/kg/day. formulas such as 100 mL/kg/day.

For example, in an 8 kg child (age 1 year) with a serum sodium level of 165 mmol/L, fluid would be administered at 1.5 times the maintenance rate, equivalent to 150 mL/kg/day (i.e., $150 \times 8 = 1200$ mL/day). Dietary volume will be 70 kcal/kg/day and this volume is incorporated in the total fluid volume. So, for this child total diet volume is $\{70 \times 8(100/67)\} = 835$ ml milk suji (As milk suji 100 ml contain 67 kcal). And correction fluid volume is $1200-835=365$ ml/day. After 24 hours if the sodium level were ≥ 150 mmol/L, the same volume will be delivered for next 24 hours.(21) This strategy represents a simplified, clinically practical method that indirectly addresses fluid deficit through augmented maintenance, without separate deficit and maintenance phases.

Rationale for the Study:

icddr,b Dhaka Hospital is the largest diarrhoeal disease hospital in Bangladesh, managing over 200,000 diarrhoea cases annually, 60% of whom are children under five. Studies conducted at icddr,b, Dhaka Hospital during two separate periods revealed that the prevalence of hyponatremia decreased from 5.1% in 2001–2002 to 2.4% in 2009–2011, while the case fatality rate increased from 15% to 19%. During this period clinical management strategies varied based on clinician preference. These included one-portion ORS and subsequent two portion water to match ongoing stool loss. Another option was to add concentrated saline to an isotonic IV fluid to create a solution with a sodium concentration at least 20 mmol/L lower than that of plasma. More

recently we are using Adroque formula with some modification. Overall, correction using ORS was significantly associated with better survival compared to those who received IV infusion.(4)

Despite a decline in its prevalence, recent data from icddr,b Dhaka Hospital showed that the case fatality rate remains as high as 19%, highlighting ongoing gaps in effective management. Clinical practice currently varies, with no universally accepted standard for the optimal type, rate, or route of fluid replacement. While gradual sodium correction is recommended to prevent cerebral oedema and seizures, existing protocols rely on formulas (e.g., Edelman, Adroque-Madias) that are primarily validated in adults and require complex calculations. Moreover, the choice between oral and intravenous fluid therapy remains debated, particularly in resource-limited settings where IV therapy carries risks of iatrogenic complications and requires intensive monitoring.

This study will address a critical gap by conducting a randomized controlled trial comparing oral and intravenous fluid therapy using the same standardized volume protocol for the correction of hypernatremic dehydration in children. By evaluating key outcomes including mortality, sodium correction rates, and neurological sequelae, the trial aims to identify a safe, effective, and context-appropriate treatment strategy that can reduce preventable deaths and long-term complications in this vulnerable population.

Research Design and Methods

Methodology

Study design: Randomized, controlled, open-label, non-inferiority trial.

Study settings: Dhaka Hospital, icddr,b

Study Population: Children under the age of five years

Study duration: 2 years

Inclusion Criteria:

1. Children of either sex with diarrhoea
2. Children with serum sodium concentration ≥ 150 mmol/L with or without symptoms
3. Parent(s) provide informed written consent for the child's participation in the study

Exclusion Criteria:

1. Children with any congenital anomaly or features suggestive of any syndrome
2. Critically ill children (e.g., septic shock, multi-organ failure) requiring inotrope or mechanical ventilation
3. Children with features of heart failure, ileus, or oedematous malnutrition
4. Any children with baseline creatinine > 5 times normal

Ethical Approval: Ethical approval for the trial will be taken from the institutional review board of icddr,b which is comprised of Research Review Committee and Ethical Review Committee.

Operational Definition:

Hypernatremia: Hypernatremia is defined as serum sodium level of ≥ 150 mmol/L and categorized as (22, 23)

- **Mild hypernatremia:** 150 -159.9 mmol/L
- **Moderate hypernatremia:** 160-169.9 mmol/L
- **Severe hypernatremia:** ≥ 170 mmol/L

Clinical manifestation of hypernatremia: Signs and symptoms of hypernatremia may consist of excessive thirst disproportionate to dehydration, restlessness, irritability, muscular twitching or jitteriness, and a high-pitched cry. Overt signs of dehydration may not be absent, but symptoms such as tachycardia, tachypnoea, a doughy skin texture, altered mental status, vacant stare, convulsion or unconsciousness may occur. Exaggerated deep tendon reflexes are also observed.

Rapid drop of serum sodium: will be defined as when there is a reduction of serum sodium of more than 12 mEq/L in any 24-hour period.

Features of raised intracranial pressure: Following a rapid drop in serum sodium, features of raised intracranial pressure include seizure, altered mental status, obtundation, coma, abnormal breathing pattern, bradycardia, and hypotension.

AKI (Acute Kidney Injury): Elevated serum creatinine (>1.5 times the reference value) considered as AKI. Normal reference value for infant 11-34 $\mu\text{mol/l}$ and for children 21-65 $\mu\text{mol/l}$. So, those who have creatinine >51 $\mu\text{mol/l}$ for infant and 97.5 $\mu\text{mol/l}$ for children was considered as AKI. Urine output $<0.5\text{ml/kg/hour}$ for at least 12 hours: (24)

Poor Neurological Outcome: Poor neurological outcome will be defined as any evidence of neurological impairment either during hospitalization or after discharge. During hospitalization, this includes a Glasgow Coma Scale (GCS) score of less than 13 persisting for more than 24 hours after stabilization, new-onset focal neurological deficits (such as paralysis or hemiparesis), or two or more seizures despite appropriate treatment. At the time of discharge, poor outcome is defined as failure to return to baseline neurological status (GCS <15) or persistence of abnormal neurological signs. Post-discharge, at 1- and 6-month follow-up visits, poor neurological outcome will be identified as developmental delay in two or more domains (gross motor, fine motor, language, personal-social) assessed by the Denver Developmental Screening Test II, or the presence of persistent motor deficits or development of cerebral palsy or epilepsy.

Shock: In this study, shock is defined as the presence of clinical signs indicating inadequate tissue perfusion in children under five years of age with diarrhoea, which may result from either hypovolemia or sepsis. This includes:

- **Hypotension:** Systolic blood pressure below age-specific cut-offs or mean arterial pressure (MAP) less than 50 mmHg.
- **Signs of poor perfusion:** Prolonged capillary refill time (>3 seconds), cold extremities, weak or absent peripheral pulses, or altered mental status (lethargy or irritability).

Nutritional Status: Nutritional status is assessed by using WHO Child Growth Standards, with Z-scores calculated for weight-for-age (WAZ), weight-for-height (WHZ), and height-for-age (HAZ). Children with Z-scores below -2 were classified as moderately malnourished, and below -3 as severely malnourished. Severe acute malnutrition (SAM) is defined as a condition in children aged 6 to 59 months characterized by any one of the following criteria: a weight-for-height or weight-for-length z-score less than -3 standard deviations (SD)

from the median of the WHO child growth standards, a mid-upper arm circumference (MUAC) of less than 11.5 cm, or the presence of bilateral pitting oedema.(25)

Hospitalization: Any post-discharge admission of the enrolled children to a hospital, with at least an overnight stay during the 6-month follow-up period, will be considered as hospitalization.(26)

Grading of Encephalopathy:

- Mild (Grade I–II): Irritability, mild lethargy, or reduced responsiveness to parents/stimuli
- Moderate (Grade III): Somnolence, intermittent responsiveness, or disorientation
- Severe (Grade IV): Unresponsiveness, stupor, or coma, with or without abnormal posturing

Seizures:

- Mild – single brief seizure (<5 minutes) without postictal confusion or to abort the seizure need single stat dose of lorazepam.
- Moderate – multiple seizures within 24 hours or prolonged seizure (5–15 minutes) with transient postictal drowsiness or need two anticonvulsants to abort the seizure.
- Severe – status epilepticus (>15 minutes) or repeated seizures without full recovery, or seizures associated with respiratory compromise or need more than two anti-convulsant to abort the seizure

Respiratory Issues:

- **Mild:** Mild tachypnea or increased work of breathing not requiring supplemental oxygen.
- **Moderate:** Respiratory distress requiring supplemental oxygen, nebulization, or non-invasive support (e.g., Bubble CPAP).
- **Severe:** Respiratory failure requiring invasive ventilation or associated with hypoxemia ($\text{SpO}_2 < 90\%$ on oxygen) or apnea episodes.

Cardiac Issues:

- **Mild:** Transient tachycardia, bradycardia, or mild hypertension/hypotension not requiring intervention.
- **Moderate:** Cardiac arrhythmias, persistent hypotension, or hypertension requiring pharmacological intervention or heart failure.
- **Severe:** Life-threatening arrhythmias, cardiac arrest, or hemodynamic instability requiring intensive care support (e.g., inotropes, resuscitation).

Sepsis, Severe Sepsis and Septic Shock: **Sepsis** was defined as suspected or proven infection with systemic signs of inflammation (e.g., fever, tachycardia, abnormal WBC count). **Severe sepsis** was sepsis with poor peripheral perfusion (e.g., hypotension, prolonged capillary refill, absent peripheral pulses) not attributable to dehydration. **Septic shock** referred to patients with severe sepsis unresponsive to two fluid boluses (@ of 20 mL/kg; maximum 30ml/kg for severe acute malnutrition (SAM) and 60 ml/kg for non-SAM) requiring inotropic support. (27)

Pneumonia: **Pneumonia** was defined according to WHO criteria as cough or difficulty breathing accompanied by fast breathing and/or lower chest wall indrawing. **Severe pneumonia** was defined as pneumonia with any WHO general danger sign, including inability to drink or breastfeed, persistent vomiting, convulsions, lethargy or unconsciousness, or stridor in a calm child.(28)

Heart failure: Suspected heart failure will be identified based on clinical findings suggestive of cardiac dysfunction, including respiratory distress or tachypnoea, persistent tachycardia disproportionate to fever or

dehydration, hepatomegaly, gallop rhythm, or other evidence of cardiac dysfunction. The diagnosis will be confirmed by the treating paediatrician or an appropriately experienced clinician, with relevant investigations performed when clinically indicated.

Ileus: Ileus will be suspected in children with abdominal distension and reduced or absent bowel sounds, particularly when accompanied by persistent vomiting, feeding intolerance, or failure to pass stool or flatus. The diagnosis will be based on clinical assessment by an appropriately experienced clinician, supported by investigations when indicated.

Oedematous malnutrition: Oedematous malnutrition will be identified by the presence of bilateral pitting oedema of nutritional origin, assessed by applying gentle thumb pressure to the dorsum of both feet for approximately three seconds and observing for persistent pitting. Alternative causes of bilateral oedema will be considered where clinically indicated.

Study procedure and patient management:

All children with acute watery diarrhoea who have a history of consuming an inappropriately prepared ORS and/or exhibit physical signs suggestive of hypernatremia will undergo screening and laboratory testing to confirm hypernatremia. If we find a child is eligible with a sodium level of ≥ 150 mmol/L, we will approach the caregiver for the consent to enrol in the study. If children present with the same history but is in shock, they will first receive standard of care treatment with a bolus of 20 mL/kg isotonic saline (Hartmann's solution) (15 ml/kg, if a child is severely malnourished). If they successful recover from shock with only fluid resuscitation then, they will be assessed for enrolment in the study.

The initial assessment will be performed by the study physician before enrolment. Suspected heart failure or ileus will be reviewed by the treating paediatrician or an appropriately experienced clinician. Relevant investigations will be obtained according to clinical need and availability; they will not be required routinely for study eligibility. The assessment findings and final eligibility decision will be documented in the screening records. Children meeting any of these exclusion criteria will not be enrolled.

After enrolment, eligible participants will be randomly assigned in a 1:1 ratio to receive either (Table 1):

- **Intravenous fluid therapy** or
- **Oral fluid therapy**

Randomization will be performed by a team not involved in the study using a computer-generated permuted block randomization sequence, and allocation will be concealed using sealed, opaque envelopes to ensure unbiased assignment.

Table 1: Plan for the fluid therapy both intravenous and oral

Parameter	Intravenous arm	Oral arm
Solution	$\frac{1}{2}$ -strength sodium acetate in 5% dextrose	WHO standard oral rehydration salt solution
Volume	1.5 $\times$ maintenance (1.5 x 100 ml/kg/day)	
Duration	24–96 hours (based on hypernatremia severity)	
Correction goal	Reduce serum sodium by no more than 0.5 mmol/L per hour and not exceeding 12 mmol/L per 24 hours	
Monitoring	Serum sodium, neurological status, weight, fluid balance	



Fig 1: Schematic representation study participant's enrolment and study work flow

Intravenous fluid therapy: For intravenous rehydration, we will use a hypotonic solution, following the *Nelson Pediatrics* guidelines for hypernatremic dehydration (21st edition) (19). The total fluid volume will be 1.5 times maintenance, administered over 24-84 hours, depending on the severity of hypernatremia. The goal is to reduce serum sodium safely, 12 mmol/L per day. Children with diarrhoea, often have metabolic acidosis, therefore, we will use ½-strength sodium acetate in 5% dextrose, instead of ½ strength normal saline. (Fig 1) This solution has osmolarity and sodium content comparable to standard 0.45% sodium chloride (½ strength normal saline) in 5% dextrose (Table 2). Acetate is metabolized to bicarbonate in the liver aiding correction of mild to moderate metabolic acidosis more effectively than chloride-based solutions.

Oral fluid therapy: For oral rehydration using ORS, we will use a standardized protocol that matches the same fluid volume calculated via the same formula, but will be administered via oral or nasogastric routes. We will use commercially available WHO recommended low osmolality ORS. The oral regimen follows the same sodium correction targets as the intravenous arm.

Both groups will undergo close monitoring of serum sodium, weight, neurological status, and fluid balance throughout the rehydration period.

Table 2: Sodium content and osmolarity of ORS, ½ strength normal saline and ½ strength Acetate or Cholera saline with 5% Dextrose in vitro (25, 29)

Solution	Sodium (Na+) (mEq/L)	Potassium (K+) (mEq/L)	Chloride (Cl-) (mEq/L)	Acetate/Citrate (mEq/L)	Glucose(g/L)	Osmolarity (mOsm/L)
WHO Low-Osmolarity ORS	75	20	65	10 (Citrate)	13.5	245
½ Strength Normal Saline + 5% Dextrose	77	-	77	-	25	~406
½ Strength IV Acetate/Cholera saline + 5% Dextrose	~67	~7	49	24 (Acetate)	25	~410

In vivo, once the dextrose is administered, it is quickly metabolized by the body's cells and converted its free water. This process leaves behind a solution of 0.45% NaCl, which is already a hypotonic solution on its own, and also adds free water. Therefore, the final effective tonicity of ½ strength normal saline + 5% dextrose or ½ strength IV acetate/cholera saline + 5% dextrose in the body is hypotonic.

All enrolled patients will receive care in the Intensive Care Unit (ICU) and will be monitored closely by the study team. Each child's clinical status will be assessed hourly, including evaluation of hydration status, consciousness level (using AVPU and Glasgow Coma Scale), vital signs, fluid balance (intake/output). Weight will be recorded every 6 hours. Detailed neurological assessments including motor and sensory evaluation, jerks and reflexes, pupillary response, and fundoscopy will be performed once daily to detect signs of cerebral oedema, haemorrhage, or other complications.

Fluid administration will be strictly guided by baseline serum sodium levels (Table 3). It will be reassessed and adjusted every 24-hour as necessary based on serial electrolyte measurements and clinical parameters such as weight changes, presence of cerebral oedema or not. If the rate of serum sodium reduction exceeds the recommended safety threshold (>12 mmol/L within 24 hours) the fluid volume will be reduced by up to 25%. More precisely if serum sodium reduces 0.5 to 0.7 mmol/L/hour the volume of the fluid will not be modified. If serum sodium decreasing rate is > 0.7 to 1 mmol/L/hour the volume of fluid will be reduced by 10-12%. If serum sodium decreasing rate is > 1mmol/L/hour then the volume of the fluid will be reduced by 20-25%. Similarly, in the event of significant weight gain (>5% within 12 hours) or clinical evidence of volume overload (weight gain, oedema) or anuria/ oliguria the fluid volume will also be reduced by up to 25%. Electrolytes will be rechecked at 6 hours, 24 hours, and then every 24 hours until normalization, or more frequently if clinically indicated. Ongoing stool output will be assessed every four hours and replaced accordingly.(30, 31)

Table 3: Optimal duration for continuing fluid therapy (13)

Serum sodium level	Expected time for fluid therapy
150 to 162mmol/L	24 hours
163-175mmol/L	48 hours
176-188mmol/L	72 hours
189-201mmol/L	96 hours

Standard of care:

Electrolyte supplementation: Serum electrolytes, including potassium and calcium, will be monitored and corrected as needed.

Micronutrients: Children with severe malnutrition will receive micronutrients, including multivitamins, zinc, and folic acid, as per standard guidelines.

Seizure control: If a child develops seizure during fluid therapy, they will be managed promptly with sequential standard anticonvulsant therapy (e.g., lorazepam, phenobarbitone or phenytoin) following established guidelines. If seizures are suspected to result from cerebral oedema, due to rapid sodium decline, 3% NaCl will be administered as per protocol (3 ml/kg over 1 hr).

Nutritional support: Age and weight-adjusted appropriate therapeutic food, without additional salt, will be provided to all children. We will provide milk suji (67 kcal /100 ml) for children aged 6 months and above. For children below 6 month we will provide modified infant formula (68 kcal /100 ml). For a breast-fed child we will continue breast feeding as expressed. Total 70 kcal/kg/day will be provided. Dietary volume will be incorporated in total fluid calculation. We will keep the record of diet volume administered meticulously. Free water intake will be restricted during the correction phase.

Antibiotics: Antibiotics will be prescribed for confirmed or suspected sepsis, pneumonia, urinary tract infection, invasive diarrhoea, or other bacterial infections, following existing icddr,b's clinical guidelines. Standard empiric antibiotics will be initiated and later adjusted based on culture results. Children with severe acute malnutrition will receive antibiotics as per standard protocols.

Switching to IV fluids instead of oral therapy:

During treatment, children may require switching to IV fluids at any stage. Indications for IV fluids initiation include:

- Circulatory collapse due to hypovolemic or septic shock
- High purging (stool output >15 ml/kg/hour)
- Persistent vomiting (≥ 3 episodes within one hour)
- Paralytic ileus causing abdominal distension with sluggish bowel sounds

Fluid selection:

- Circulatory collapse and high purging: Isotonic fluids (Hartmann's solution, Acetate, Normal saline) for rapid correction.
- Persistent vomiting or paralytic ileus: 0.45% normal saline with 5% dextrose.

Regular follow-up: Dehydration status, mentation of the patient (AVPU, GCS scale), vital signs, weight change, input-output chart, calorie intake, associated condition status, neurological examination (pupil, reflex and jerk), fundoscopic examination (any haemorrhage, blurred optic disc) will be done periodically.

The study team responsible for the management of enrolled children will dedicated solely to this project, rather than the regular ICU staff. This will ensure consistent and standardized care for all participants, minimizing variability in clinical management. The dedicated team will strictly follow the study protocol for fluid therapy, monitoring, and other interventions, which will maintain uniformity in treatment across both study arms and enhance the reliability of study outcomes.

Referral outside: Patients will be referred to a tertiary hospital for dialysis if hyponatremia is complicated by persistent renal impairment, evidenced by elevated creatinine (>5 times the age-specific upper limit) or low urine output (<0.5 ml/kg/hour for > 12 hours).

Neurodevelopmental Evaluation and Follow-Up After Hospital Discharge: Following hospital discharge, patients will be followed up in a structured schedule. Initial follow-up will be conducted via telephone at 3 days and 2 weeks post-discharge to assess the child's general condition, provide support to caregivers, and identify any early concerns. Any events of hospitalization during the follow-up period will be recorded.

Subsequent physical follow-up visits will be scheduled at 1 month (± 7 days) and 6 months (± 7 days) post-discharge. At each of these visits, a comprehensive neurodevelopmental assessment will be performed using the Denver Developmental Screening Test II (DDST-II).(32)

These assessments will be conducted by a trained pediatrician experienced in administering and interpreting the DDST-II, a standardized tool used to assess developmental progress in children from birth to 6 years of age across the following four domains:

1. Gross motor skills (e.g., sitting, walking)
2. Fine motor-adaptive skills (e.g., grasping, object manipulation)
3. Language (e.g., responding to sound, speaking)
4. Personal-social behavior (e.g., smiling, interacting)

This structured follow-up approach is designed to identify early signs of developmental delay and ensure timely intervention and support.

Laboratory Investigations:

Name of the test	Time
Serum Electrolytes and creatinine	At base line, 6 hours after initiation of fluid therapy, then daily until sodium level normalize
Serum osmolarity	At base line and upon recovery
Urine Electrolyte, osmolarity, specific gravity	
BUN	
CBC	At base line

Adverse events monitoring: Participants enrolled in the hypernatremia fluid therapy study will be closely monitored for both general and serious adverse events throughout hospitalization and follow-up. General adverse events include phlebitis, abdominal distension, hyperkalemia, volume overload, rapid decline in serum sodium concentration, seizure, cerebral oedema, acute kidney injury (AKI), pneumonia, sepsis, septic shock, re-hospitalization and healthcare-associated infections (HAI). Serious adverse events (SAEs) are defined as life-threatening or fatal outcomes, including respiratory failure requiring mechanical ventilator support and death. All adverse events will be documented, assessed for severity and potential relationship to the study intervention and managed according to standard clinical protocols. Any SAE identified during the study will be reported to the Data and Safety Monitoring Board (DSMB) within 24 hours of notification and reviewed promptly to ensure participant safety.

Sample Size Calculation and Outcome (Primary and Secondary) Variable(s)

Sample size calculation:

This non-inferiority open-label RCT calculated sample size to assess whether oral fluid therapy is not inferior to intravenous therapy in reducing under-five mortality. Based on a retrospective data from Dhaka Hospital, icddr,b, the mortality rate in this population is estimated at 19%. A non-inferiority margin of 6% was pre-specified, representing the maximum allowable difference in mortality that would still consider oral therapy clinically acceptable compared to intravenous therapy.

Assuming a one-sided alpha level of 0.05, a power of 80%, and equal allocation between groups (1:1), the minimum required sample size was calculated to be 244 children (122 per group). To account for an anticipated 10% attrition rate due to loss to follow-up, early withdrawal, or protocol violations, the final sample size was increased to 268 participants, with 134 children in each arm. This sample size ensures sufficient power to detect non-inferiority in mortality outcomes between the two fluid therapy modalities.

This following formula has been used for calculation of sample size:

$$\text{Non-inferiority} \quad \pi_1 - \pi_2 \geq \delta \quad n_i = \frac{(z_\alpha + z_\beta)^2 (\pi_1(1-\pi_2) + \pi_2(1-\pi_1))}{(\pi_1 - \pi_2 - \delta)^2}$$

Table 4: Calculation of Sample Size

Indicators		Information	Comment
Proportion of outcome in group receiving IV fluid therapy	π_2	0.19	Literature
Reduction	%	30%	Defined by User
Proportion of outcome in group receiving oral fluid therapy	π_1	0.13	Calculated value
Non-inferiority margin	δ	0.06	
Beta	β	0.20	Defined by User
Alpha	α	0.05	
Power	$1-\beta$	0.80	Calculated value
Z alpha value	Z_α	1.64	
Z beta value	Z_β	0.84	
Sample size for one group	n	122	
Attrition	%	10%	Defined by User

Sample Size for each group	n_adj	134	Calculated value
Total sample size	n	267	

Outcome variables:

Primary Outcome: All-cause mortality from initiation of the intervention until hospital discharge among children under five years of age with hypernatremic dehydration associated with diarrhoea.

Primary outcome measures: Events of death any time during hospitalization after initiation of intervention until discharge.

Secondary Outcomes:

1. Incidence of rapid serum-sodium reduction (>12 mmol/L in 24 h)
2. Need for ancillary interventions (e.g., 3% NaCl, anticonvulsants)
3. Frequency of abnormal weight gain
4. Acute kidney injury (AKI) events
5. Poor neurological outcome at 1 and 6 months
6. 6-month all-cause mortality

Secondary outcome measures:

1. Serum sodium level at different time points
2. Incidence of convulsions and use of anti-convulsant and 3% NaCl during the rehydration period
3. Weight at every 6-hour follow-up
4. Serum creatinine level at different time points
5. neurodevelopmental outcomes (cerebral oedema, developmental delay) at hospital and during follow-up visits
6. Case fatality at 6-month follow-up

Data Analysis

Data analysis plan:

Data entry and analysis will be done using the SPSS for Windows (Version 20.0. Armonk, NY: IBM Corp and Epi Info (version 7.0, USD, Stone Mountain, GA). Data will be analyzed using both intention-to-treat (ITT) and per-protocol (PP) approaches to assess the robustness of findings. Descriptive statistics will summarize baseline characteristics, clinical parameters, and outcomes. Categorical variables (e.g., mortality, convulsion events) will be compared using the Chi-square test or Fisher's exact test, while continuous variables (e.g., rate of sodium correction, weight changes) will be analyzed using the Student's t-test or Mann-Whitney U test, depending on data distribution. A non-inferiority analysis will be performed for the primary outcome

(mortality), using risk difference with a 95% confidence interval; non-inferiority will be concluded if the upper limit of the confidence interval does not exceed the pre-specified margin of 6%. To identify predictors of poor neurological outcome at discharge, 1 month, and 6 months after initiation of treatment, data on potential risk factors including baseline demographics, clinical features (such as severity of hyponatremia, dehydration, and seizures), laboratory parameters, and treatment variables will be analyzed using multivariable logistic regression to determine independent predictors. In addition, exploratory analyses will be conducted to examine factors associated with mortality, including illness duration, severity at presentation, and the presence of comorbidities, to better understand potential predictors or contributors of mortality. Logistic regression will be employed to adjust for potential confounders. A p-value <0.05 will be considered statistically significant. After reaching 50% of the target sample size, if data and safety monitoring board (DSMB) feels, a midterm analysis will be conducted. If the difference between the intervention groups yields a p-value of less than 0.001 with a 99.7% confidence interval, the study will be stopped early, following the Peto and Fleming approach.(33)

Data Safety Monitoring Plan (DSMP)

The Data and Safety Monitoring Plan (DSMP) for this study ensures the rigorous oversight of clinical trial procedures to safeguard participant safety and maintain data integrity. Given the high fatality and neurological risks associated with hyponatremic dehydration in children under five, continuous monitoring of fluid therapy, electrolyte levels, and patient outcomes is essential. Investigators will conduct periodic assessments of participant recruitment, retention, and treatment efficacy while ensuring adherence to protocol guidelines. Close surveillance of serum sodium correction rates will be maintained to prevent rapid drops that may lead to cerebral oedema and neurological complications. Hourly clinical evaluations and frequent electrolyte assessments will be conducted to guide fluid adjustments, minimizing treatment failure and adverse effects. Through these measures, the DSMP will provide a structured framework to uphold the safety of participants and the validity of study findings.

To further enhance trial oversight, an independent data and safety monitoring board (DSMB) will be formed. They will assess data safety, protocol adherence and will identify any emerging concerns or the need for protocol modifications. This structured approach ensures that participant safety remains the top priority while preserving the scientific validity of the trial.

Ethical Assurance for Protection of Human rights

This study will be conducted among human participants to evaluate the outcomes of different fluid therapy modalities in hyponatremic children with diarrhoea. Informed written consent will be obtained from caregivers before participation. The study will strictly adhere to the ethical principles outlined in the Helsinki Declaration, ensuring beneficence, nonmaleficence, autonomy, and justice. Participants' anonymity and confidentiality will be maintained throughout the study, and participation will remain entirely voluntary, allowing caregivers or patients to withdraw at any stage without consequence. If the collected data is used for future research, no identifiable personal information will be accessible to researchers, ensuring complete privacy and ethical integrity.

Use of Animals

Not Applicable

Collaborative Arrangements

We will collaborate with the Department of Paediatric Nephrology at Bangladesh Child Hospital & Institute (Professor Dr. Shireen Afroz) and the Department of Paediatric Nephrology and Child Health at Bangladesh

Medical University (Professor Dr. Sayed Saimul Huque). They will contribute to the development of the full protocol and provide technical oversight throughout the study.

Facilities Available

The study will be conducted at the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh. This hospital is located in Dhaka city, the capital of Bangladesh. It provides care and treatment to around 200,000 diarrhoeal patients with or without associated complications and with or without other health problems each year. The vast majority of the patients come from poor socioeconomic backgrounds from urban and peri-urban Dhaka, the capital city of Bangladesh. This hospital has an ICU equipped with mechanical ventilation and other facilities of management of critically ill patients, as well as properly trained clinical staff to provide care to young patients. At the ICU, critically ill children receive treatment of severe pneumonia, convulsion, meningitis, electrolyte imbalance and septic shock.

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Protocol No. PR-25040	Version No. 1.1	Date: 9.23.2025
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Protocol Title: Oral Versus Intravenous Fluid Therapy for Hypernatremic Dehydration in Children Under Five with Diarrhoea: A Randomized Controlled Non-Inferiority Trial”

Investigator’s name: **Dr Haimanti Saha**

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b)

Purpose of the Research

This study aims to compare different fluid therapy modalities to establish the most effective protocol for treating hypernatremia in children under five years of age suffering from diarrhoea.

Background

Hypernatremia is a condition where the sodium level in the blood becomes abnormally high, often due to incorrect preparation or intake of oral rehydration salt (ORS) solutions. It can have severe clinical effects, including neurological complications and even death. The best method for rehydrating hypernatremic children is still debated. This study will evaluate different fluid therapy approaches to determine the safest and most effective treatment for affected children.

Why You Are Invited to Participate

Your child has been diagnosed with hypernatremia (Serum sodium level ≥ 150 mmol/L) and falls within the under-five age group targeted in this study. As a caregiver/guardian, we invite you to participate in this research to help improve paediatric healthcare.

Methods and Procedures

If you agree to participate, the following procedures will be followed:

- Your child will be randomly assigned to one of the fluid therapy modalities being tested.
- Regular monitoring will be conducted to assess the treatment's effectiveness.
- All medical care will be provided by trained professionals at Dhaka Hospital, icddr,b.

Risks and Benefits

Risks: Participation in this study involves minimal risk. However, there may be a small chance of complications related to fluid therapy, which will be carefully monitored and managed by medical professionals.

Benefits: Your child will receive high-quality medical care under the supervision of experienced healthcare professionals. The findings from this study may help improve treatment strategies for hypernatremic children in the future.

Privacy, anonymity, and confidentiality

Your child's personal identification and collected clinical information will be confidential and the documents of your participations will be preserved in a secure place (locked file cabinet under lock and key), under the responsibility of the principal investigator. As we will value your and your child's anonymity and privacy, your patient will be identified by a number. No one except the study staff, members of the Ethical Review Committee of the Centre will have access to the records.

Future use of information

If the data or information collected from you (in relation to your patient's health conditions), will be used for future research purposes, that information will be unidentifiable and utilized by obtaining ethical clearance from the Ethical Review Committee of the icddr,b.

Right not to participate and withdraw

It will be your voluntary decision whether your patient will participate in our study or not. Even if you don't agree to allow your patient to participate, he/she will receive equal standard care and treatment of the icddr,b. You can withdraw your patient's participation in at any part of the study without any reasoning and still your child will be supported with the same healthcare facilities in the Dhaka Hospital, icddr,b.

Principle of compensation

In an unlikely event such as any injury that occurs to your patient during the participation in this study, you will be provided best possible, free treatment, for research related injuries. You will not have to pay to us, and we will also not pay to you for participating in the study.



Informed Consent Form for Parent/Guardian of Under-five Children

Protocol No. PR-25040	Version No. 1.3	Date: 1-06-2026
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Protocol Title: “Oral Versus Intravenous Fluid Therapy for Hypernatremic Dehydration in Children Under Five with Diarrhoea: A Randomized Controlled Non-Inferiority Trial”

Investigator’s name: Dr Haimanti Saha

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b)

If you agree to our proposal for enrolling you/your patient in our study, please put ✓ mark on appropriate box(es) of the following and finally sign on the specified place for you:

I have read the participant’s information sheet version 1.3. dated 01.06.2026, have had the opportunity to ask question, discuss the study, and received satisfactory answers.

Yes ☐ No ☐

I understand that I am free to leave the study without giving any reason.

Yes ☐ No ☐

I understand that the information I give is confidential.

Yes ☐ No ☐

I agree to my identifiable data being used for future ethically approved studies.

Yes ☐ No ☐

I agree to being contacted in the future for studies related to this research.

Yes ☐ No ☐

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the sponsor and by regulatory authorities, where it is relevant to my taking part in this research.

I give my permission for those individuals to have access to my records. Yes ☐ No ☐

I agree to provide sample of my child's blood, urine, stool, and other biological specimens. Yes ☐ No ☐

I agree to bring my child for follow-up visit

Yes ☐ No ☐

I give my consent to take part in the study.

Yes ☐ No ☐

Signature or left thumb impression and name of Guardian

Date

Signature or left thumb impression and name of the witness

Date

Signature and name of the PI or his/her representative

Date

Communication:

If you have any question, you can ask me right now or at any time later to the below mentioned personnel:

Purpose of contact	Name and address	Address for communication
For any question related to the study, or any problem	Dr. Haimanti Saha (local coordinator or representative)	Address: icddr,b, Dhaka Hospital, Mohakhali, Dhaka-1212 Mobile No: 01712217742
	Dr. Haimanti Saha (name of PI)	Address: icddr,b, Dhaka Hospital, Mohakhali, Dhaka-1212 Mobile No: 01712217742
To know the rights or benefits or to log any complain or dissatisfaction	Ms. Sabina Shahnaz (IRB Coordinator)	IRB Secretariat, Research Administration, icddr,b, Mohakhali, Dhaka-1212 Phone: 02-222277084 or Mobile: 01716599329

Thank you for your cooperation.