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Bicarbonate for AcidosiS in very pretErm babies: a randomised clinical trial: The BASE Trial

Submission date
03/10/2023

Recruitment status
Recruiting

Registration date
06/11/2023

Overall study status
Ongoing

Last Edited
07/03/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Metabolic acidosis is a build-up of acid in the bloodstream which has various causes. In the UK, 8,000 babies are born very preterm each year and many will develop metabolic acidosis during their stay in a neonatal unit. Sodium bicarbonate is widely, but not universally, used to treat metabolic acidosis in very preterm babies but the evidence underpinning its use is poor. Some doctors believe that giving sodium bicarbonate lowers acid levels in the bloodstream and improves the functioning of the heart, but others believe sodium bicarbonate raises acid levels in the cells of the body which can be harmful in the short and long-term by affecting blood flow to the brain and other tissues in the body. The two approaches of using sodium bicarbonate, or not, for episodes of metabolic acidosis are commonly used across the UK, so there is nothing new about either type of care. The reason practice differs widely is that the impact and effectiveness of sodium bicarbonate in very preterm babies have never been properly studied. The study team want to answer the question, 'In very preterm babies with metabolic acidosis, does treating them with sodium bicarbonate or not impact their health and development in the short and long term?'

Who can participate?
Very preterm babies with metabolic acidosis

What does the study involve?
In this study, 3,764 babies will be allocated at random to either routine use of sodium bicarbonate infusion or no routine use of sodium bicarbonate infusion. The study will compare survival to discharge from neonatal care without the occurrence of major illnesses during neonatal care between the two groups to find out whether giving sodium bicarbonate or not affects very preterm babies' health in the short term. Babies will also be followed up until they are 24 months of age and corrected for prematurity to assess whether there are any longer-term effects of giving sodium bicarbonate or not on children's development.

Sodium bicarbonate is widely, but not universally, used in the management of metabolic acidosis in very preterm babies despite a very low grade of evidence underpinning its use. The BASE

study will be the first adequately powered trial to study the impact and effectiveness, both in the short and long term, of the use of sodium bicarbonate to treat metabolic acidosis in very preterm babies.

The two trial arms being compared both represent existing clinical practice in different neonatal units in the UK, i.e.:
• routine use of sodium bicarbonate infusion for episodes of metabolic acidosis
or
• no routine use of sodium bicarbonate infusion for episodes of metabolic acidosis

What are the possible benefits and risks of participating?
Use of verbal consent
As both interventions are already in routine clinical practice, the trial will use a verbal consent approach. This is designed to keep the study as simple as possible, make it easier for babies to take part and minimise the burden on parents. Acceptability by UK research ethics committees and parents of consent approaches that do not include a written consent form has been demonstrated, as well as feasibility in recent and ongoing neonatal trials (WHEAT Pilot, WHEAT International and neoGASTRIC trials). Parents in three focus groups conducted during the development of the BASE trial application indicated that consent models which do not include a written consent form would be their preferred method in the immediate period after preterm delivery. Parents will be provided with trial information by members of the clinical care team in the antenatal period or during neonatal admission prior to randomisation. Paper and electronic patient information sheets will be provided and trial information videos and animation will be available online. Parents of eligible babies will be approached by a member of the neonatal team. Parents will confirm if they are willing for their baby to participate in the study during a verbal conversation with site staff. It will be documented in the baby's medical notes that information about the study has been provided to the parents and verbal consent has been obtained. A Verbal consent approach means that there will not be a signed consent form. Verbal consent will be documented in the baby's medical notes and Investigator Site File (ISF) and this will be checked before randomisation.

Data collection
The majority of trial data will be obtained from routinely recorded clinical data held in the National Neonatal Research Database (NNRD), which will reduce the burden of data collection for participating sites. Babies will remain allocated to the same care pathway until they reach 40 weeks postmenstrual age or are discharged from neonatal care (whichever is sooner). No data collection is required by parents whilst their baby is in neonatal care. Final follow-up assessment by parent questionnaire will be conducted at 24 months of age corrected for prematurity. Neurodevelopmental outcomes at 24 months of age corrected for prematurity will be collected remotely via a parent questionnaire completed electronically using a bespoke secure online trial questionnaire. Alternative methods will be offered for those not wishing to complete online, i.e. on paper via a postal questionnaire or over the telephone with a member of the trial team. Parents will also be given the option of completing the questionnaire over the telephone via Language Line translation services where they do not read or speak English sufficiently enough to complete the questionnaire. A multi-language handout will be provided when contacting parents to inform them of the option to use translation services through the BASE coordinating centre.

Parents of all surviving participants will be contacted by the trial team to complete the questionnaire when their child reaches 24 months of age (corrected for prematurity). Contact and reminders will be made by email, text message and post. Parents will be informed about this in the Parent Information Leaflet.

Where possible, before discharge from the neonatal unit, a discussion will take place with parents to remind them about follow-up and that the trial team will contact them at 24 months of age corrected for prematurity for parent-reported outcome data. In the event that parents do not complete a 24-month questionnaire or if there is missing data, routine clinical data relating to the child's 24-month clinical follow-up assessment will be requested from sites for assessment by the Blinded Endpoint Review Committee (BERC) to classify neurodevelopmental outcome.

Use of a cannula
Most babies who develop metabolic acidosis are likely to have a cannula as part of routine care. However, occasionally when a baby does not have a cannula, the placement of a cannula in order to administer sodium bicarbonate would be required. Parents will be informed in the Parent Information Leaflet (PIL) that this may happen if their baby is allocated to routine use of sodium bicarbonate infusion arm.

Where is the study run from?
Imperial College London, Faculty of Medicine, School of Public Health (UK)

When is the study starting and how long is it expected to run for?
September 2023 to March 2029

Who is funding the study?
National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme

Who is the main contact?
Prof Sabita Uthaya, s.uthaya@imperial.ac.uk (UK)

Study website
https://www.npeu.ox.ac.uk/base

Contact information

Type(s)
Public, Scientific

Contact name
Miss Catherine Thompsett

Contact details
Trial Manager
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National Perinatal Epidemiology Unit (NPEU)
Nuffield Department of Population Health
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Type(s)
Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007672

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 1007672, CPMS 56448

Study information

Scientific Title
Bicarbonate for AcidosiS in very pretErm babies: a randomised clinical trial: The BASE Trial

Acronym
The BASE Trial

Study objectives
Sodium bicarbonate is widely, but not universally, used to treat metabolic acidosis in very preterm babies but the evidence underpinning its use is poor. The BASE trial aims to answer the question, ‘In very preterm babies with metabolic acidosis, does giving them sodium bicarbonate or not impact their health and development in the short and long term?’

The primary objective of the BASE trial is to evaluate the effect of sodium bicarbonate on survival to discharge from neonatal care without major morbidity.

Babies will also be followed up until they are 24 months of age corrected for prematurity to assess whether there are any longer-term effects of giving sodium bicarbonate or not on children's development.

The trial will also look at the impact of sodium bicarbonate on death and individual major morbidities during neonatal care, duration of neonatal unit stay and acceptability to parents.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/11/2023, East Midlands – Nottingham 2 Research Ethics Committee (Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048169; nottingham2.rec@hra.nhs.uk), ref: 23/EM/0244

Study design
Randomized controlled open-label parallel-group study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital, Internet/virtual, Medical and other records, Telephone

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Metabolic acidosis

Interventions
Two trial arms are being compared:
1. Routine use of sodium bicarbonate infusion for episodes of metabolic acidosis (intervention)
2. No routine use of sodium bicarbonate infusion for episodes of metabolic acidosis (control)

Babies will remain allocated to the same trial arm until they reach 40 weeks postmenstrual age or are discharged from neonatal care (whichever is sooner).
During their neonatal unit stay, babies can have more than one episode of metabolic acidosis, defined as blood pH less than 7.2 with pCO2 that is low or normal for the clinical context and a low bicarbonate level. Once randomised to an arm, all subsequent episodes of metabolic acidosis (unless in the context of cardiopulmonary resuscitation) will be as per the randomised allocation.

Investigational medicinal product used for intervention arm:
Neonatal Intensive Care Unit (NICU) stock of sodium bicarbonate for intravenous infusion.
The dosage and duration of infusion will be decided by the treating clinician.

Randomisation:
Randomisation of babies to either trial arm will be managed via a secure web-based

randomisation facility hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (University of Oxford) with telephone backup available at all times (365 days per year). A senior Trials Programmer at the NPEU CTU will write the web-based randomisation program and hold the allocation codes. The Senior Trials Programmer and Senior Statistician will monitor the implementation of the randomisation procedure throughout the trial. Randomisation will occur as soon as a baby becomes eligible, using a 1:1 allocation ratio.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Sodium Bicarbonate [Sodium bicarbonate injection]

Primary outcome measure
Primary objective:
To evaluate the effect of sodium bicarbonate on survival to discharge from neonatal care without major morbidity in preterm babies with metabolic acidosis.

Primary outcome measures:
Survival without major morbidity, with major morbidity defined as any of the following up to discharge from neonatal care or 40 weeks postmenstrual age (whichever is sooner):
1. Bronchopulmonary dysplasia (BPD) (defined as any respiratory or ventilatory support or supplemental oxygen at 36 weeks postmenstrual age)
2. Treatment for retinopathy of prematurity (ROP) (defined as cryotherapy, laser therapy or injection of anti-VEGF therapy for retinopathy of prematurity in either or both eyes)
3. Major brain injury (grade 3 / 4 IVH, periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention)
4. Late-onset sepsis (defined as one or more episodes of a positive blood or cerebrospinal fluid culture with either a pure or mixed growth of a known pathogenic organism after the first 72 hours following birth)
5. Severe necrotising enterocolitis (defined as necrotising enterocolitis confirmed at surgery)
6. Major surgery (defined as any major surgical procedure recorded during neonatal admission)

Secondary outcome measures
Key secondary objective:
To evaluate the impact of sodium bicarbonate on survival without moderate to severe neurodevelopmental impairment at 24 months of age corrected for prematurity.
Secondary outcome measure:
Survival without moderate to severe neurodevelopmental impairment, including gross motor, vision and hearing impairment measured using a validated parent-report questionnaire, and cognitive and language impairment measured using the Parent Report of Children’s Abilities - Revised (PARCA R) at 24 months of age corrected for prematurity

Other secondary objectives:
To evaluate the impact of sodium bicarbonate on death and individual major morbidities during

neonatal care, duration of neonatal unit stay and acceptability.
Other secondary outcome measures:
1. Death up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
2. Bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age
3. Treatment for retinopathy of prematurity up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
4. Major brain injury (grade 3 / 4 IVH, periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention) up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
5. Late-onset sepsis up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
6. Severe necrotising enterocolitis (necrotising enterocolitis confirmed at surgery or resulting in death) up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
7. Major surgery up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
8. Pulmonary haemorrhage resulting in increase in ventilatory requirements or blood transfusion (described using summary statistics only) up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
9. Receipt of invasive respiratory support (described using summary statistics only) at 36 weeks postmenstrual age
10. Receipt of non-invasive respiratory support (described using summary statistics only) at 36 weeks postmenstrual age
11. Duration of intensive care (level 1 care as defined by BAPM) as a proportion of total length of stay in the neonatal unit up to discharge from neonatal care or reaching 40 weeks' postmenstrual age (whichever is sooner)
12. Total length of stay in neonatal care up to discharge from neonatal care or reaching 40 weeks' postmenstrual age (whichever is sooner)
13. Change in weight z-scores in survivors (described using summary statistics only) Between birth and discharge from neonatal care or 36 weeks postmenstrual age (whichever is sooner)
14. Receipt of mother's own breast milk up to discharge from neonatal care or reaching 40 weeks' postmenstrual age (whichever is sooner)

To describe the patterns of sodium bicarbonate usage:
Dosage and duration of sodium bicarbonate infusion (described using summary statistics only) up to discharge from neonatal care or reaching 40 weeks' postmenstrual age (whichever is sooner)

Other secondary outcomes:
1. Known death by 24 months of age corrected for prematurity
2. Moderate to severe neurodevelopmental impairment at 24 months of age corrected for prematurity
3. Components of moderate to severe neurodevelopmental impairment (gross motor, vision, hearing, cognitive and language; presented descriptively) at 24 months of age corrected for prematurity

Overall study start date
29/09/2023

Completion date

31/03/2029

Eligibility

Key inclusion criteria
1. Babies born between 23+0 and 30+6 weeks+days of gestation inclusive
2. Postmenstrual age less than 34+0 weeks+days
3. Metabolic acidosis defined as blood pH less than 7.2 with pCO2 that is low or normal for the clinical context and a low bicarbonate level
4. The parent's verbal consent for the baby to participate in the trial has been documented in the baby's medical notes and Investigator Site File

Participant type(s)
Patient

Age group
Neonate

Lower age limit
0 Weeks

Upper age limit
6 Weeks

Sex
Both

Target number of participants
3764

Key exclusion criteria
1. Life-threatening condition, or significant congenital anomaly
2. Inborn error of metabolism (known or under active investigation)
3. Prior treatment with sodium bicarbonate unless in the context of cardiopulmonary resuscitation or if used as a substitute for normal saline in arterial line infusion.
4. Current episode of metabolic acidosis immediately follows cardiopulmonary resuscitation

Date of first enrolment
20/02/2024

Date of final enrolment
01/07/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Arrow Park Hospital
Arrowe Park Road
Wirral
United Kingdom
CH49 5PE

Study participating centre
Birmingham Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5SS

Study participating centre
Chelsea & Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Burnley General Hospital
Casterton Avenue
Burnley
United Kingdom
BB10 2PQ

Study participating centre
Leicester Royal Infirmary
Infirmary Square

Leicester
United Kingdom
LE1 5WW

Study participating centre
Lincoln County Hospital
Greetwell Road
Lincoln
United Kingdom
LN2 5QY

Study participating centre
Bedfordshire Hospitals NHS Foundation Trust
Lewsey Road
Luton
United Kingdom
LU4 0DZ

Study participating centre
Medway Maritime Hospital
Windmill Road
Gillingham
United Kingdom
ME7 5NY

Study participating centre
The Royal Wolverhampton NHS Trust
New Cross Hospital
Wolverhampton Road
Heath Town
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
Queens Medical Centre, Nottingham University Hospital
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Princess Royal Hospital
Apley Castle,
Grainger Drive
Apley
Telford
United Kingdom
TF1 6TF

Study participating centre
Queens Hospital
Rom Valley Way
Romford
United Kingdom
RM7 0AG

Study participating centre
Bolton Royal Hospital
Minerva Road
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Royal United Hospitals Bath NHS Foundation Trust
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
St Helier Hospital
Wrythe Lane
Carshalton
United Kingdom
SM5 1AA

Study participating centre

Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Royal Oldham Hospital
Rochdale Road
Oldham
United Kingdom
OL1 2JH

Study participating centre
The Tunbridge Wells Hospital
Tonbridge Road
Pembury
Tunbridge Wells
United Kingdom
TN2 4QJ

Study participating centre
Watford General Hospital
60 Vicarage Road
Watford
United Kingdom
WD18 0HB

Study participating centre
William Harvey Hospital
Kennington Road
Willesborough
Ashford
United Kingdom
TN24 0LZ

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney
Norwich

United Kingdom
NR4 7UY

Study participating centre
Pinderfields General Hospital
Aberford Road
Wakefield
United Kingdom
WF1 4DG

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Sponsor information

Organisation
University of Oxford

Sponsor details
National Perinatal Epidemiology Unit (NPEU)
Nuffield Department of Population Health
Old Road Campus
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base@npeu.ox.ac.uk

Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Submission to regulatory authorities
5. Other

Data Sharing requests can be made at the end of the research in line with the NPEU Data sharing policy

Intention to publish date
31/03/2030

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the National Perinatal Epidemiology Unit, University Of Oxford ctu@npeu.ox.ac.uk; Chief Investigator, Dr Sabita Uthaya s.uthaya@imperial.ac.uk. All or a subset of participant data collected during the study will be shared, excluding any contact details. If any identifiable data is required, approval from the Confidentiality Advisory Group of the Health Research Authority (CAG) will be required before sharing any data. Data will be available after the results have been published. Verbal consent will be obtained from parents to join the study. Parents will be informed prior to providing consent about data sharing within the Parent Information Leaflet. The dataset will be de-identified before sharing, and consideration will be given to the required level of de-identification, which will be in line with the departmental anonymisation and de-identification policy and guidance. Appropriate ethical approvals must be in place, and a

data-sharing agreement between the two parties agreed upon before any data is shared. Datasets will only be shared with researchers who provide a scientifically sound proposal, there is adequate funding for the proposed work, and there is an appropriate ethics committee and other approvals in place as required or in progress (data will not be released until appropriate approvals are in place) and the analysis will be performed and/or supervised by an appropriately qualified statistician/researcher.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	09/02/2024	24/02/2024	No	No