The KIND study
The supplementation of Ketones in Neurological Damage: A pilot randomized controlled trial

A single-centre pilot randomised trial to determine the feasibility of ketone ester supplementation in addition to standard care, compared with placebo and standard care to improve neurological outcomes in neurocritical care patients admitted to the ICU

Investigators:

Dr. Matt Anstey
Dr. Brad Wibrow
Ms Emma Osnain
Dr. Vanessa Carnegie

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1. Abbreviations

ICU	Intensive Care Unit
KE	Ketone Ester
KB	Ketone Body
BHB	Beta Hydroxybutyrate
ACAC	Acetoacetate
BSL	Blood Sugar Level
RCT	Randomised Controlled Trial
AE	Adverse Event
SAE	Serious Adverse Event
SAH	Subarachnoid Haemorrhage
TBI	Traumatic Brain Injury
ICP	Intracranial pressure
CPP	Cerebral perfusion pressure
HIE	Hypoxic-ischaemic encephalopathy

2. Lay Summary

Acute brain injury

There are a wide range of diseases that lead to brain injury in patients admitted to the intensive care unit. These diseases include bleeding in the brain due to a variety of causes as well as diseases that lead to a loss of adequate blood supply to the brain and death of brain cells. The patients who suffer from this spectrum of diseases and acute brain injury are often young and, if they survive, have a high burden of disability and the impacts of this on their own lives as well as the lives of their loved ones and the community.

Current therapies in ICU to support these patients focus on ways to increase oxygen and blood supply to damaged parts of the brain but little research to date has been done looking at how we can increase the energy supply to the brain.

Previous research also indicates that the acutely injured brain may struggle to use glucose – the brain's usual energy supply – adequately and that this can worsen the damage that has already occurred to brain cells. Therefore, it is important to find alternative fuels the brain can use instead in periods of stress and disease.

Ketone bodies as an energy source for the brain

Ketone bodies are by-products of the body's metabolism of fat and are a known alternative fuel for many tissues in the body in times of stress. Previous research has also shown that ketone bodies may be useful in other neurological conditions such as epilepsy, and animal as well as human models of brain disease have suggested that they may be a useful energy source in times of stress including acute brain injury.

Traditionally, humans have increased ketones in the bloodstream by way of a specialized diet called the ketogenic diet, though this process can often take up to many days. There is increasingly interest in the use of dietary supplementation of ketones as a faster way to achieve increased ketone levels in the body.

Purpose of the study

The aim of this study is to determine the feasibility of giving ketone bodies in the form of dietary supplementation to patients with acute neurological injury admitted to ICU in order to improve neurological outcomes.

Study design

This study will use be a randomised controlled trial, a well known study design that eliminates study biases that can confound findings as much as possible in order to determine the true utility of the use of ketones in brain injury. Patients who are in a coma with an acute brain injury, admitted to ICU, will be eligible to participate in this trial.

Participants will be randomised (like the toss of a coin) to routine administration of ketone bodies via a feeding tube on admission and standard care, or placebo and standard care alone. Ketone body supplementation is currently not available for ICU patients and will only be available within this trial.

Study importance

Determining the feasibility of giving ketone bodies to patients with acute brain injury admitted to ICU is the first important step in a program of research that ultimately aims to test the efficacy of using ketone bodies in this group of patients to improve neurological outcomes and reduce morbidity.

3. Synopsis

3.1 Background

Altered cerebral glucose metabolism likely contributes to tissue hypoxia and secondary neurological injury in patients admitted to ICU with acute brain injury due a variety of aetiologies. Ketosis may be an alternative energy source in times of cerebral starvation and this has been classically achieved through the ketogenic diet. Enteral supplementation of ketone bodies in the form of ketone esters may be a quicker way to achieve ketosis in this population and are safe and easily available as over-the-counter dietary supplements. This trial will assess the feasibility of administering ketone esters via the nasogastric route in patients admitted to ICU with coma and either subarachnoid haemorrhage or hypoxic-ischaemic encephalopathy as a critical step in a programme of research aimed at determining the role of ketone body supplementation in patients with acute brain injury in the ICU.

3.2 Aim

The primary aim is the determine the feasibility of a trial of ketone ester administration in patients with coma (GCS < 8) and either SAH or HIE admitted to ICU.

The secondary aims are to measure:

1. Proportion of patients achieving ketosis in the blood with blood ketone levels > 2mmol/L
2. CSF values of lactate and ketones where a study participant has an EVD in situ
3. Levels of serum S100B (brain injury marker)
4. Adverse side effects including acidosis, dysglycemia, intracranial hypertension and reduced cerebral perfusion pressure
5. Modified Rankin scale at three months post-discharge

3.3 Hypothesis

The primary hypothesis is that a trial of ketone ester administration to improve neurological outcomes in patients admitted with acute brain injury to ICU is feasible on the basis of compliance with this study protocol.

3.4 Methods

We will conduct a single-centre, pilot RCT of patients admitted to ICU with coma (GCS < 8) and either SAH or HIE. All such patients who are 18 years and above old, mechanically ventilated and have a nasogastric tube, who are able to receive KE supplementation within eight hours (and ideally four hours) will be eligible to be enrolled in the trial. After consent is obtained, participants will be randomised in a one-to-one ratio to either KE ester supplementation via NGT and standard care or placebo and standard care. Data will be collected through a study-specific case report form (CRF) and participants followed up until three-months post-enrolment.

3.5 Outcomes

Primary outcome will be feasibility of implementing a trial of KE supplementation in patients admitted to ICU with acute neurological injury. Feasibility will be achieved if all of the following outcomes are met:

1. Less than or equal to 50% of patients (or their proxies) refuse to participate on the basis of concerns over ketone administration
2. Greater than or equal to 80% of patients randomised to ketone ester supplementation receive them within the first eight hours of ICU admission

Secondary outcomes will include:

1. Percentage of patients achieving ketosis in blood (ketones > 2)
2. Description of CSF values – lactate, ketone levels (note this will only be performed if an extra-ventricular drain (EVD) is in situ so patients will not be exposed to additional invasive tests as part of this study
3. Level of serum S100B (brain injury marker)
4. Adverse side effects (acidosis, dysglycemia, intracranial hypertension, reduced cerebral perfusion pressure).
5. Modified Rankin scale at 3 months following discharge.

4. Background and Rationale

4.1 Altered cerebral glucose metabolism contributes to secondary neurological injury

Astrocytes produce and store glycogen but in limited amounts and rely on a steady supply of both glucose and oxygen to support their metabolic needs. Blood glucose levels are tightly controlled and uptake across the blood brain barrier occurs via the GLUT-1 transporter. When metabolized in the brain, glucose produces lactate and pyruvate and is the main substrate for energy metabolism. (1)

In various forms of brain injury seen in the critically ill, there is evidence of deranged or dysfunctional cerebral glucose metabolism and this can contribute to tissue hypoxia and cell death and therefore worse neurological outcomes for patients. (1)

In TBI, PET studies demonstrate an overall reduction in cerebral glucose metabolism uncoupled from cerebral blood flow. In addition, there is an overall increase in cerebral glucose demand from baseline. These processes result in a relative glucose deficiency as an energy substrate and altered ability of the brain to metabolise glucose.
(2)

4.2 Ketones are an alternative energy substrate for neurons

Ketone bodies are a metabolic product of fat metabolism and are produced in hepatic mitochondria. The three ketone bodies are acetoacetate (AcAc), acetone, and betahydroxybutyrate. Acetylcoenzyme A is formed by beta oxidation of free fatty acids and is the precursor to AcAc which is the central ketone body. (3)

Ketogenesis usually occurs during times of starvation and can supply up to 50% of the body's basal energy requirements as well as up to 70% for the brain. (3) (4)

While the brain usually relies on glucose as its main energy substrate, during periods of starvation it can adapt to the use of ketones as its main energy source. (2) (5)

The rate of ketone utilization is usually a function of circulating plasma levels. In health, with an intact blood brain barrier, the cerebral uptake of ketones is limited by diffusion as well as the ability of the monocarboxylic acid transporters (MCT1 and MCT2) to transport them across the blood brain barrier. However, there is evidence that in states of neurological injury, there are rapid changes in vascular and cellular transporters that facilitate increased ketone body uptake and metabolism. There is also evidence to suggest that in times of oxidative stress, the brain can adapt from relying on glucose as its primary energy substrate to using ketone bodies instead. (3) (6; 7) (8) (9) (10)

4.3 The use of the ketogenic diet and ketone supplementation has been shown to be of benefit in other patient populations with neurological disease and in animal models of acute brain injury

The efficacy of the ketogenic diet has long been established in paediatric populations with refractory status epilepticus and is now also being explored in other neurological conditions including neurodegenerative conditions such as Alzheimers disease. (11) (12) Two recent studies have also demonstrated feasibility and safety in inducing ketosis using the ketogenic diet in traumatic brain injury. (13) (14) (15)

Studies in animal models of the ketogenic diet and of exogenous ketone supplementation have also shown promise in acute neurological injury. (16) (17) (18)

4.4 Dietary ketone supplements are safe and readily available as over-the-counter preparations

Ketone bodies can be supplemented in the form of ketone salts or as ketone esters (KE) in solution. KE supplements are more easily tolerated with less gastrointestinal upset and fewer adverse metabolic side effects than ketone salt solutions, including fewer incidents of hypernatremia. (19) Current research directions include the production and study of intravenous ketone bodies to provide acute supplementation but this research is still in very early stages and is not yet widely available for research or clinical application.

KE solutions are readily available as an over-the-counter dietary supplement from multiple manufacturers in North America. (20) (21)

5. Study Design

5.1 Overall Study Design

This is a single centre randomised controlled trial that will determine the feasibility of conducting a definitive trial examining the administration of ketone esters to patients administered to the ICU with severe neurological injury

5.2 Aim

The aim of this study is to determine feasibility of administering a trial of ketone esters in patients admitted to the ICU with severe neurological injury

5.3 Hypothesis

The primary hypothesis is that a definitive randomised trial of ketone ester administration is feasible on the basis of recruitment rate and compliance with study protocol.

The secondary hypothesis is that the administration of ketones will not result in significant adverse drug reactions including acidosis, dysglycemia and alterations to measures such as intracranial pressure and cerebral perfusion pressure.

5.4 Eligibility Criteria

Patients are eligible for enrolment if they meet all of the inclusion criteria and none of the exclusion criteria

5.5 Inclusion Criteria

Any patient, intubated and mechanically ventilated with a nasogastric tube, within 8 hours of admission who is anticipated to survive at least 72 hours with the following:

1. Patients with subarachnoid haemorrhage with an admission GCS less than or equal to 8

2. Patients admitted following out of hospital cardiac arrest who are intubated with a GCS less than or equal to 8

5.6 Exclusion Criteria

1. Age < 18 years old
2. Pregnant
3. Suffering from Acute or Chronic liver disease
4. Type 1 diabetes mellitus
5. Treating clinician determines that the administration of ketone esters is inappropriate for the patient
6. Base of skull fracture precluding insertion of NGT

5.7 Recruitment process

All of the patients eligible for this study, by definition will lack capacity to provide consent. Consent will be obtained using the Guardianship Administration Act Amendment, independent medical practitioner pathway. For this research study to have efficacy, the time frame for administration of the ketone ester is short (with the rationale that it may be helping injured brain), and as such, as we will aim to use both "Medical Research with consent of Research Decision-Maker and "Urgent Medical Research without consent" processes. In such patients, where legally permissible, their surrogate decision-maker, will be approached to provide informed consent prior to participation in the study. We will aim to gain consent within four hours of presentation to hospital, and if the "Research Decision-Maker is not available in that time frame, then proceed along the Urgent Medical Research without consent pathway. Consent to ongoing participation will be sought from all participants who regain capacity as soon as practicable to Consent and will be approached for prospective informed consent as participants.
[https://rgs.health.wa.gov.au/Documents/GAA%20Medical%20Research%20Guidance%20Document.pdf]

5.8. Randomisation and treatment allocation

Patients will be randomized only after signed informed consent has been obtained or a decision to proceed along the urgent medical research without consent pathway as above. Randomisation will occur in a 1:1 ratio and occur as soon as possible following admission to the Intensive Care Unit. Randomisation will be derived from a computer-generated random number sequence. Allocation concealment will be maintained using sequential opaque sealed envelopes stored in the ICU.

As a pilot feasibility study, 10 patients in each group with be enrolled (total 20 patients).

5.9 Study treatments

Following enrolment, trial participants will be randomised to receive either nasogastric administration of ketone esters within 8 hours of ICU admission in addition to standard care or standard care and nasogastric administration of placebo.

Participants randomised to KE supplementation
Trial participants randomised to KE supplementation will have this preparation administered via nasogastric tube within eight hours of ICU admission.

Dose: 40g bolus (40mL of ketone esters followed by 10g/hr (10ml/hr) NG infusion of KE for 12 hours OR NG administration of placebo (water) and subsequent infusion for 12 hours.

The dose is based on pharmacokinetic studies that suggest 26.8g of a ketone monoester in healthy individuals three times a day will induce ketosis, without any adverse effects on blood glucose, lipids or electrolyte results. (22)

Communication with the manufacturer suggests that a weight-based dose may be necessary across different body compositions, and their own testing suggests a dose between 20-40g is sufficient, with more GI upset (nausea) experienced above 45g. To simplify between adjusting the dose for different patients, we have selected 40g bolus.

Product: The KE supplement is a clear, colourless liquid solution that comes packaged in plastic bottles. It is manufactured by Health Via Modern Nutrition Inc, USA under the brand name, Ketone-IQ. It can be administered via syringe or an enteral feeding set down the participants nasogastric tube by ICU nursing or medical staff.

Participants randomised to placebo
Trial participants randomised to placebo will have this administered via nasogastric tube within eight hours of ICU admission (ideally within 4 hours of hospital presentation). The placebo substance will be sterile water prepared in similar bottles by the same company.

5.10 Outcome measures

The primary outcome will be study feasibility. The study will be deemed feasible if all of the following criteria are met:

1. Less than or equal to 50% of patients (or their proxies) refuse to participate on the basis of concerns over ketone administration
2. Greater than or equal to 80% of patients randomised to ketone ester supplementation receive them within the first eight hours of ICU admission

Secondary outcomes will include

1. Percentage of patients achieving ketosis in blood (ketones > 2)
2. Description of CSF values – lactate, ketone levels (note this will only be performed if an extra-ventricular drain (EVD) is in situ so patients will not be exposed to additional invasive tests as part of this study
3. Level of serum S100B (brain injury marker)
4. Adverse side effects (acidosis, dysglycemia, intracranial hypertension, reduced cerebral perfusion pressure).
5. Modified Rankin scale at 3 months following discharge.

5.11 Data collection

All data will be collected by trained data collected onto paper source documents, developed specifically for the study. Data will be entered into a database stored securely in a password protected file on a computer in the ICU.

Data collection will be restricted to those variables required to define baseline patient characteristics, delivery of the intervention, and concurrent treatment, and study outcomes. Participants will be followed up until discharge from the ICU.

Data to be collected will include:

- Baseline patient data

    - Patient identifiers
    - Demographics including BMI and gender
    - Inclusion and exclusion criteria
    - Concurrent medical diagnoses
- Diagnosis
- GCS on presentation
- Interventions
    - Presence of EVD
    - Presence of intraparenchymal ICP monitor
- Neurophysiological variables
    - Average intracranial pressure following ketone ester administration within 24 hours (mmHg)
    - Worst ICP following KE administration within 24 hours (mmHg)
    - Average cerebral perfusion pressure following ketone ester administration within 24 hours (mmHg)
    - Worst CPP following KE administration within 24 hours (mmHg)
- Other physiological variables
    - ABG values at 4, 8, and 24 hours post ketone ester administration, specifically
        - pH
        - Base excess
        - Bicarbonate
        - Blood glucose
        - Lactate
    - Blood ketone levels at 4, 8 and 24 hours post-ketone ester administration
    - CSF ketone, lactate levels at 4, 8 and 24 hours post-ketone ester administration (if EVD in situ)
    - s100B protein levels (serum) at enrolment, and 24 hours following enrolment
    - NG aspirates (mL)
    - Nursing recording of bowel motions
- Follow-up at 3 months – phone call to administer modified Rankin Scale score.

6. Ethics

6.1 General Principles

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki, the ICH GCP Notes for Guidance on Good Clinical Practice and the NHMRC National Statement on Ethical Conduct in Research Involving Humans.

6.2 Hospital Research Ethics Committee Approvals

Hospital research ethics committee (HREC) approval will sought prior to enrolling study participants.

6.3 Consent

Eligible participants will be identified as early as possible after fulfilling inclusion criteria. Patients will be enrolled after informed consent is obtained and no data collection will occur until consent has been obtained. All information will be submitted completely de-identified.

6.4 Confidentiality of Patient Data

The research coordinator will compile an enrolment log containing the patient initials, date of birth and date of screening. This will be kept separately from the study data. For patients enrolled in the study, study data will be identified by the unique study number only. Study data will be entered initially on paper forms. All paper copies of study data will be kept in a study file in a locked office in the ICU. Study data will be entered into a password-protected database on a computer in the ICU.

7. Data Collection

7.1 Data Collection Methods

Data will be collected after patient consent is obtained and the participant is randomised to a study arm and until ICU discharge. An enrollment log will be kept in the ICU containing the medical record number and unique study identifer to allow identification of each patient for study-related correspondance and data entry.

7.2 Data Variables Collected

A summary of the case report form (CRF) is located in the appendix, definition the study periods and data collection required.

7.3 Data Management

Data will be collected by trained research co-ordinators at SCGH. Patients and/or their next of kin will be asked to provide two possible points of contact (home and close family contact details) to the research staff prior to discharge. Day 30 (post hospital discharge) modified Rankin Scale will be conducted over the phone by a trained assessor.

Study data will be entered directly into a secure web-based case report form (using RedCAP) with the option to print blank and completed forms.

Once the study is completed, paper records will be shredded and electronic database will be destroyed 15 years after the completion of the study. Only authorised study personnel will have access to the electronic database. At the time of study completion, computer records will be copied to a compact disc for long term storage and back up.

8. Adverse Events

Adverse events will be collected as free text.

8.1 Serious Adverse Events (SAEs)

Specific serious adverse events to be collected include:

1. Dysglycemia.
   It is possible that provision of KE could change blood glucose levels (although in healthy volunteer trials this has not been seen), so QID BSLs will be monitored for the duration the patient receives the KE
2. Abnormalities in acid-base status (patients will have arterial lines, and arterial blood gases are taken as part of standard care, which can evaluate serum sodium, pH and lactate)
3. Serious gastrointestinal upset (defined as diarrhoea, vomiting)

8.2 Reporting

SAEs will be recorded on a separate CRF. SAEs that occur from time of commencement of study treatment to discharge from ICU will be reported to the project officer by emailing (within the encrypted hospital webmail system) the SAE form. All SAEs should be reported as soon as possible and within 24 hours of study staff becoming aware of the event. Minimum information to report will include the patient initials and study number, nature of the event, when the event occurred and the duration, investigator's opinion of the relationship between study involvement and the event and what treatment was administered for the event.

8.3 Data safety monitoring board

This is a small pilot study and no DSMB will be formed for the purposes of the study. However, all SAEs will be reported to the HREC within 24 hours of notification.

9. Statistical analysis plan

9.1 Sample size

The sample size has been selected to determine future feasibility of conducting a larger trial.

9.2 Analysis plan

This is a descriptive study but will involve comparisons between the two cohorts of patients. Baseline and clinical data will be summarised using non-parametric medians and interquartile ranges, due to small group sizes. Between-group comparisons will be analysed using Kruskall Wallis H tests. Categorical data will be described using frequencies and percentages and compared between groups using Chi-squared or Fischer's Exact tests, as appropriate.

10. Publication

The study will be conducted by Drs. Matthew Anstey, Bradley Wibrow, and Vanessa Carnegie and Ms Emma Osnain. The principle publication from the study will be in the name of these investigators with full credit assigned to all collaborating investigators, research coordinators, and the institution. Funding bodies will be acknowledged in the publication.

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