Liberal Glucose Control in Critically Ill Patients With Pre-existing Type 2 Diabetes (LUCID)

Management Committee

Mr Alex Poole – University of Adelaide PhD candidate

Associate Professor Adam Deane, Dr James Anstey, Professor Rinaldo Bellomo, Dr Vishwanath Biradar, Associate Professor Glenn Eastwood, Professor Simon Finfer, Dr Mark Finnis, Dr Palash Kar, A/Prof Craig French, Dr Mathew Maiden, Professor Colin McArthur, Professor Shay McGuinnes, Dr Paul Secombe, Dr Anthony Tobin, A/Prof Peter Kruger, Associate Professor Andrew Udy
LUCID

‘Showing ability to think clearly, especially in the intervals between periods of confusion or insanity ’
Outline

1. Background
2. Relevance of T2DM?
3. Preliminary data
4. Phase II study
5. Longer term objectives
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Abnormally elevated blood glucose levels occur frequently (30-40\%) in the critically ill. This may reflect diabetes (type 1 or more frequently type 2) or ‘stress hyperglycaemia.'
The New England Journal of Medicine

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINGKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOULLON, M.D., PH.D.

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*
‘Bad’ glucose protocols are harmful

Implementation of protocols directing glucose normalization might potentially have been responsible for ~26,000 deaths per year in the US alone

Brian Kavanagh (AJRCCM 2016)
Current guidelines for management of hyperglycaemia

American Diabetes Association (2018)

Critically Ill Patients
- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, a glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended for the majority of critically ill patients. A
- More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia. C

Society for Critical Care Medicine (2012)

Recommendations: The article is focused on a suggested glycemic control end point such that a blood glucose $\geq 150$ mg/dL triggers interventions to maintain blood glucose below that level and absolutely $< 180$ mg/dL. There is a slight reduction in mortality with
Current practice
Survey of ANZ intensivists

- Insulin commenced when blood glucose ≥ 10 mmol/L, and titated to maintain blood glucose between 6.0-10 mmol/L
- Insulin usually administered intravenously
- Uncertainty about optimal management of hyperglycaemia in T2DM in ICU
- Equipoise to conduct a randomised control trial

Poole et al ACC 2018.
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Individuals adapt to their conditions

‘It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change’

Charles Darwin
Prevalence of T2DM

- In 2012 about 12% of the Australian population had diabetes
  - Between 11-35% of all hospitalised patients have diabetes
- Prevalence in critical care is 12-40%
- 30,000 patients with diabetes admitted to ICU per year
- By 2030 439 million people will be living with diabetes (mainly T2DM)
- Annual cost $490 billion USD
Potential adverse effects of insulin treatment?

- Hypoglycaemia
- Glycaemic variability
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Effects of hyperglycaemia in ICU patient with diabetes

- Retrospective (Egi, 2011)
- Prospective cohort studies (Plummer, 2014)
Effects of hyperglycaemia in ICU patient with diabetes

- Post-hoc analysis of RCT (van den Berghe, 2006)

- Prospective, sequential period studies (Di Munzo 2016, Kar 2016 and Luethi 2018)
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Hypothesis

- A higher glycaemic threshold for use of insulin will:
  - Primary – Attenuate moderate and severe hypoglycaemia (blood glucose <3.9 and <2.2 mmol/L) and recurrent hypoglycaemia
  - Secondary – diminish glycaemic variability
Patients

Inclusion criteria
- >18 years old
- Will be in ICU until the day after tomorrow
- Artline or Central line
- Has diabetes
- Reasonable likelihood BGL ≥10 mmol/L

Exclusions
- Death inevitable
- Admitted with diabetic ketoacidosis or hyperosmolar state
- Type 1 diabetic
- Specific BGL target
- Eating within 24 hours
- In ICU for >24 hours
- Pregnant
Intervention

Blood glucose (mmol/l)

Target range

Rx Insulin

Liberal

Control
Study outcomes: Processes

- Recruitment rate
- Consent withdrawal rate (delayed consent)
- Protocol adherence
- Treatment separation
- Point-of-care HbA1c measurement
- Insulin requirements
Study outcomes: Scientific

- Hypoglycaemia (number and severity)
- Relative hypoglycaemia
- Glycaemic variability
- Time weighted mean glucose
Study outcomes: Exploratory

- 90 day mortality
- 28 day ICU free days
- signal for harm with regards to infection
- weakness
- feed-intolerance
Power calculations

- Pilot data – Hypoglycaemia (Kar, et al.)
  - RR 0.47 (95% CI, 0.19-1.13)
- NICE-SUGAR – Hypoglycaemia (standard)
  - Conventional (blood glucose 6-10 mmol/L) and hypoglycaemia (17.5%)
- Sample size 426 ($\beta$ 0.8; $\alpha$ 0.05; $\Delta$ 9.5) round up to 450
Progress of LUCID

- HREC approval obtained
- Funding from
  - Royal Adelaide Hospital
  - Diabetes Australia
  - Intensive Care Foundation
  - Melbourne Academic Centre for Health
- eCRF and web based randomisation developed
- Recruitment commenced May 2017
Progress of LUCID

• 10 Sites currently recruiting
  Royal Adelaide Hospital  Royal Melbourne Hospital  Alice Springs Hospital
  Lyell McEwin Hospital  Geelong Hospital  Austin Hospital
  Princess Alexandra Hospital  Alfred Hospital  St Vincent’s Hospital Melbourne
  Western Hospital Melbounre

• 7 sites to commence
  Auckland DHB General ICU  Auckland Hospital CVICU  Flinders Medical Centre
  Royal North Shore Hospital  Logan Hospital  Vincent's Hospital Sydney, NSW
  Wellington

• 193 participants have been randomised

• Recruitment to be completed by May 2019
1. Background
2. Why are we interested in T2DM?
3. Preliminary data
4. Phase II study
5. Long term objective
Implications of LUCID

• Inform current practice
• Provide feasibility information
• Further safety information on the intervention
• Stimulate larger RCT
Longer term objective

- A definitive, phase III, open label, parallel group RCT comparing ‘liberal’ glucose targets and ‘standard care’ in critically ill patients with type 2 diabetes
- Primary endpoint: 90-day mortality
Questions?

We are seeking additional sites

Please contact: Alexis.Poole@Adelaide.edu.au
0414 515 123