Original articles

Safety and Feasibility of an Insulin Adjustment Protocol to Maintain Blood Glucose Concentrations Within a Narrow Range in Critically Ill Patients in an Australian Level III Adult Intensive Care Unit

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ABSTRACT

Objective: *Recent data have shown a link between normal blood glucose levels and improved outcomes in intensive care patients. We wished to develop an insulin adjustment protocol for an adult intensive care unit to maintain blood glucose concentrations safely within a narrow range.*

Methods: *After a 6 month introductory period, an observational study was conducted during a 10 month period in an Australian level III intensive care unit to assess the safety and feasibility of an insulin adjustment protocol to maintain blood glucose concentrations safely within a narrow range. The protocol included a variable insulin infusion, a constant caloric source and frequent blood glucose level monitoring to detect and prevent hypoglycaemia.*

Results: *Over the 10 month period a total of 148 patients were studied using the protocol and represented 13 % of all intensive care unit admissions during this period. In total, there were 12,623 patient hours 'on protocol', with 5,603 blood glucose levels performed. The mean morning blood glucose level was 6.5 mmol/L and 49% of blood glucose levels were within the target range of 4.1 - 7.0 mmol/L. There were four recorded incidents of hypoglycaemia, defined as a blood glucose level of less than 2.2 mmol/L, the lowest at 1.5 mmol/L being the only symptomatic episode. The incidence of hyperglycaemia (blood glucose level > 10 mmol/L) was 13 % of all blood glucose level measurements.*

Conclusions: *The insulin adjustment protocol with a constant caloric source and frequent blood glucose level monitoring was found to be safe and feasible in maintaining blood glucose concentrations within a narrow range in a mixed adult intensive care unit population.* (**Critical Care and Resuscitation 2004; 6: 92-98**)

Key words: Critical illness, intensive care, critical care, glucose, insulin, protocol, audit

Hyperglycaemia and insulin resistance are common in critically ill patients, and an associated increase in morbidity and mortality have been described in hyperglycaemic patients following cardiac surgery, burns, and acute myocardial infarction.[1-8] Maintenance of normoglycaemia in the critically ill patient has

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received renewed attention following a recent randomised clinical trial reporting decreased morbidity and mortality in intensive care unit (ICU) patients treated with intensive insulin therapy and tight glycaemic control compared with conventional management of blood glucose levels (BGL's).[9]

However, maintaining BGL's at a lower concentration in ICU patients can lead to an increased likelihood of hypoglycaemia. We wished to develop an insulin adjustment protocol to maintain blood glucose concentrations within a narrow range in an adult intensive care unit population, while also maintaining safety, particularly concerning the detection and prevention of hypoglycaemia in sedated or unconscious patients.

The purpose of this study was to review, after a 6-month trial period, the safety and feasibility of an insulin adjustment protocol to maintain blood glucose concentrations within a narrow range in a mixed adult ICU population.

METHODS

During a 6-month trial period, an insulin adjustment protocol was developed in an adult 14 bed medical, general and cardiac surgical intensive care unit to maintain the blood glucose level (BGL) range between 4.4 - 7.0 mmol/L. The development of the protocol involved ongoing modifications in response to 3 monthly audits and feedback from nursing and medical staff regarding problems with the protocol design. At the end of this period, the insulin adjustment protocol was established for clinical use in our intensive care unit.

All patients admitted to the Geelong Hospital ICU, who were managed using the insulin adjustment protocol for more than 6 hours during a 10-month period from June 2002 to April 2003 were included in the study. The insulin adjustment protocol was used when the patient's BGL exceeded 7 mmol/L. The protocol was discontinued when the patient resumed oral intake or ceased continuous enteral or parenteral caloric intake. Exclusion criteria included admission for diabetic ketoacidosis, non-ketotic hyperglycaemic coma, or other primary hyperglycaemic conditions requiring individualised insulin management. Treating physicians were able to remove patients from the trial at their discretion.

The target BGL range was 4.4 - 7.0 mmol/L, with adjustments to the insulin infusion rate performed according to the protocol. The design of the protocol aimed to alter the insulin infusion rate up or down in relation to the absolute BGL and rate of change of the BGL. Intensive care nurses performed blood glucose measurements at regular intervals which ranged from 30 minutes to 4-hourly depending on the stability and level of BGL. Actrapid® (Novo Nordisk Pharmaceuticals Pty, Ltd, Bagsvaerd, Denmark) insulin (50 units mixed with 0.9% saline to 50 mL in a 50 mL syringe) was infused using Alaris Asena™ syringe pump (Alaris® Medical Systems Inc, San Diego, CA). Blood glucose measurements were whole-blood measurements performed using a blood gas analyser (ABL-625, Radiometer, Copenhagen, Denmark).

A specific feeding regime was not introduced as part of the protocol and enteral nutrition, parenteral nutrition, and maintenance intravenous fluids were prescribed at the discretion of the ICU physicians. The insulin adjustment protocol required patients to have a constant caloric source to prevent hypoglycaemic events. Patients receiving enteral or parenteral nutrition were prescribed 5% or 10% dextrose solutions during periods when nutrition was withheld. Details of the protocol are shown in the attached appendices.

Clinical information collected included admission category, APACHE II score, length of stay, and mortality. Blood glucose levels and changes to insulin infusion rates were recorded on a data collection sheet. The morning BGL's were recorded as the lowest BGL measured between 6:00 and 9:00 am each day. Data were entered into a spreadsheet (Microsoft Excel© 2000). Analyses according to length of stay in ICU and admission category were performed. For each group, distribution of BGL's and average morning BGL's were recorded.

RESULTS

Of the 1,201 patients admitted to the ICU during the 10 month study period, 160 (13%) were treated with the insulin adjustment protocol. The insulin adjustment protocol was discontinued in five patients, two of whom were insulin dependent diabetics who reported symptoms of hypoglycaemia at BGL's in the target range and three of whom had periods of resistant hyperglycaemia. All five patients were excluded from the current study. A further seven patients had incomplete recording on datasheets and were excluded from the study. The remaining 148 patients were included in the current study.

The clinical characteristics of the 148 patients on the insulin adjustment protocol are shown in Table 1. The mean APACHE II score was 19 and the hospital mortality was 14.2 % for patients on the insulin adjustment protocol, compared with a mean APACHE II of 17 and a hospital mortality of 11.1 % for all ICU admissions during the study period.

The 148 study patients were on the insulin adjustment protocol for a total of 12,623 hr (526 days) and underwent a total of 5,603 BGL measurements. There were 4 recorded BGL's of less than 2.2 mmol/L (1.5, 2.1, 2.1, 2.1) and 43 BGL's within the range varying

between 2.2 - 3 mmol/L. All BGL's of less than 2.2 mmol/L occurred in conscious patients who were on the insulin adjustment protocol for greater than 5 days. The only symptomatic hypoglycaemic episode recorded occurred in a patient who had a BGL of 1.5 mmol/L. A total of 2746 BGL's (49%) recorded were within the target range of 4.1 - 7 mmol/L, and 744 BGL's (13%) recorded were greater than 10 mmol/L (Table 2).

Table 1. APACHE II score, ICU and hospital mortality and length of stay in the 148 insulin adjustment protocol patients

APACHE II score (mean ± SD)	19 ± 5
ICU mortality number (%)	14 (9.5)
Hospital mortality number (%)	21 (14.2)
Mean ICU length of stay in days	6.4

ICU = intensive care unit

In patients who were on the insulin adjustment protocol for less than 24 hr, 213 (40%) of their BGL's were in the target range, with 107 (20%) of BGL's greater than 10 mmol/L. For patients who were on the insulin adjustment protocol for more than 5 days, 1890 (51%) BGL's were within the target range, and 458 (12%) BGL's were greater than 10 mmol/L. The average morning BGL was 6.45 ± 2.1 mmol/L (Table 2). Data for patients grouped by admission category are shown in Table 3.

DISCUSSION

The aim of this study was to assess the safety and feasibility an insulin adjustment protocol to maintain blood glucose concentrations within a narrow range in a mixed adult intensive care unit population. The safety of the insulin adjustment protocol was primarily determined by the prevention and detection of hypoglycaemia and its attendant complications. While in a conscious patient, hypoglycaemia can be defined as a low BGL associated with its characteristic signs and symptoms which are relieved when the blood glucose is elevated,[11] in the unconscious and critically ill patient, the clinical features, in particular, may be masked. During the 6-month pilot period preceding the study, 3 symptomatic hypoglycaemic episodes occurred in a population of 42 ICU patients. All episodes occurred following the cessation of enteral or parenteral nutrition or dextrose solutions, while the insulin infusion continued. The danger of continuing an insulin infusion after ceasing either enteral or parenteral nutrition, or dextrose infusions was recognised and the insulin adjustment

Table 2. Blood glucose levels in patient groups according to length of time on protocol

	Total	≤ 1 day	1 – 5 days	> 5 days
Number of patients	148	64	59	25
Hours on protocol	12623	976	3001	8646
BGL measurements	5603	539	1348	3716
BGL's < 2.2 (mmol/L)	4	0	0	4
BGL's 2.2 – 3.0 (mmol/L)	43	2	11	30
BGL's 3.1 – 4.0 (mmol/L)	192	12	43	137
BGL's 4.1 – 7.0 (mmol/L)	2746	213	643	1890
BGL's 7.1 – 10.0 (mmol/L)	1874	205	472	1197
BGL's > 10.1 (mmol/L)	744	107	179	458
Morning BGL (mean ± SD mmol/L)	6.45 ± 2.1	6.90 ± 2.06	6.3 ± 2.05	6.43 ± 2.12

BGL's = blood glucose levels

Table 3. Mean morning blood glucose level, highest admission blood glucose level and clinical characteristics according to admission category

	Cardiac surgical	*General medical*	*General surgical*
Number	82	38	28
APACHE II score (mean ± SD)	17 ± 4	22 ± 6	20 ± 5
Morning BGL (mean ± SD mmol/L)	6.66 ± 2.23	6.35 ± 2.16	6.31 ± 1.80
Duration on the protocol (hr)	51.05	139.76	111.64
Hospital mortality (%)	4.9	30.8	17.9

BGL = blood glucose level

protocol was subsequently modified.

A plasma glucose concentration of 2.5 - 2.8 mmol/L is often quoted as the range, below which, symptoms of hypoglycemia occur. If whole blood glucose concentrations (which have values 15 - 20% lower than plasma glucose levels)[11] are used, symptoms of hypoglycemia may occur at values less than 2.2 mmol/L. However, the symptoms of neuroglycopaenia may not be predicted by plasma glucose levels alone, and can be influenced by other factors including recent glucose control and fasting.[11,12]

In animal models of hypoglycaemia, neuronal damage occurs only after EEG isoelectricity is achieved, with the density of neuronal necrosis related to cerebral isoelectricity rather than BGL's.[13] In one study of adult-onset insulin dependent diabetic patients, a history of one or more hypoglycaemic coma episodes (median 3, range 1 - 35) in 55 patients was not associated with any difference in cognitive function when compared with 53 patients who had no history of hypoglycaemic coma episodes.[14] These findings challenge the model of defining clinically significant hypoglycaemia at a set BGL, and also illustrate the current uncertainty about the long term neuronal effects of symptomatic hypoglycaemic episodes.

In the ICU patient the clinical diagnosis and significance of hypoglycaemic episodes are difficult to determine, as the signs and symptoms can be masked by sedation, other causes of reduced consciousness, and the autonomic stress responses. In one study of 554 critically ill patients, when hypoglycaemia was defined as a BGL of less than 2.2 mmol/L, there were 39 (7%) episodes of hypoglycaemia, 2 of which were symptomatic.[9] In another study of 38 critically ill patients, no episodes of hypoglycaemia were recorded using an insulin adjustment protocol when hypoglycaemia was defined as a BGL less than 3.0 mmol/L.[15]

In the current study of 148 patients there were 4 (2.7%) episodes of hypoglycaemia, defined as a BGL less than 2.2 mmol/L. In a total of 12,623 patient hours during the insulin adjustment protocol, this represented one BGL value of less than 2.2 mmol/L in every 131 patient days. All hypoglycaemic episodes occurred in patients who were on the insulin adjustment protocol for more than 5 days. A single episode was associated with symptoms of sweating and reduced level of consciousness at a BGL of 1.5 mmol/L. We observed that BGL instability often followed periods when enteral or parenteral nutrition was interrupted and appeared to be due either to the introduction of intravenous dextrose or cessation of the insulin infusion. The protocol was considered to be safe when compared with previously published studies.[9,15]

Previous studies have used a mean morning BGL to indicate the 'tightness' of glycaemic control, and reported mean morning BGL's of 5.7 mmol/L,[9] and 7.6 mmol/L.[15] In the current study we recorded a mean morning BGL of 6.5 mmol/L. The most obvious difference in our protocol when compared with other studies was the target BGL range. The target range was 4.4 - 7.0 mmol/L in our study, compared with 4.4 - 6.0 mmol/L (mean morning BGL of 5.7 mmol/L)[9] and 5.0 - 8.0 mmol/L (mean morning BGL of 7.6 mmol/L)[15] in other studies. These results suggest the mean morning BGL will tend towards the upper end of the target BGL range.

Establishing the best BGL range is difficult due to the lack of evidence regarding the safe lower limit of blood glucose in sedated patients and the efficacy or otherwise of higher BGL target ranges. In previous studies, the most effective insulin adjustment protocol as measured by the lowest mean BGL also had the highest number of hypoglycaemic episodes.[9] No studies have determined outcomes with higher mean BGL's, or used different measures to assess efficacy (e.g. BGL control over a 24 hr period). A post-hoc analysis of a recent large randomised intensive insulin therapy trial concluded there was no lower limit of blood glucose below which no further risk reduction occurred.[10]

Our study found that the introduction of a insulin adjustment protocol to maintain a BGL range between 4.4 - 7.0 mmol/L was safe and feasible. Safety was achieved by combining insulin infusions with a constant caloric intake and frequent BGL monitoring.

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APPENDIX 1

BLOOD GLUCOSE PROTOCOL NON-INSULIN DEPENDENT/NON-DIABETIC

- **INSULIN INFUSION MUST BE STOPPED IMMEDIATELY IF CONTINOUS CALORIC INFUSION (i.e. PARENTERAL NUTRITION, ENTERAL FEEDS or 5-10% DEXTROSE) STOPPED, INTERRUPTED, OR NOT ABSORBED**

- **PATIENTS ON ORAL DIET MUST HAVE INSULIN INFUSION CEASED IMMEDIATELY CONTINOUS CALORIC SOURCE CEASED**

- **INSULIN INFUSION CANNOT BE INCREASED MORE OFTEN THAN 4 HOURLY**

BGL < 2.6 mmol/L
- Cease actrapid infusion if running
- Intravenous bolus 25 mL x 50% dextrose
- Review current dextrose infusion, enteral, parenteral nutrition
- Measure BGL every 30 minutes or more frequently if symptomatic until > 4.4 mmol/L

BGL 2.6 - 4.3 mmol/L
- Reduce infusion rate by 2 units/hr
- Review current dextrose infusion, enteral, parenteral nutrition
- Measure BGL every 30 minutes or more frequently if symptomatic until > 4.4 mmol/L

BGL 4.4 - 7.0 mmol/L
- If BGL decreased > 2 mmol/L in last 4 hr reduce infusion rate by 1 units/hr
- If BGL decreased ≤ 2 mmol/L or increased in last 4 hr continue insulin infusion at existing rate
- Measure BGL 2-hourly x 2, then 4-hourly until BGL leaves target range (4.4-7.0 mmol/L)

BGL 7.1 - 10 mmol/L
- Insulin rate cannot be increased more often than 4-hourly
- If first BGL, then commence infusion at 1unit/hr
- If BGL decreased > 2 mmol/L in last 4 hr continue insulin infusion at existing rate
- If BGL decreased ≤2 mmol/L or increased in last 4 hr, increase infusion rate by 1 unit/hr
- Measure BGL at 2-hourly (to detect rapid decrease in BGL)

BGL > 10 mmol/L
- Insulin rate cannot be increased more than 4-hourly
- If first BGL start at 2 unit/hr
- If BGL decreased > 2 mmol/L, continue insulin infusion at existing rate
- If BGL decreased ≤2 mmol/L or increased, increase infusion rate by 2 unit/hr
- Measure BGL at 4-hourly

APPENDIX 2

BLOOD GLUCOSE CONTROL PROTOCOL INSULIN DEPENDENT DIABETICS

- **INSULIN INFUSION MUST BE STOPPED IMMEDIATELY IF CONTINOUS CALORIC INFUSION (i.e. PARENTERAL NUTRITION, ENTERAL FEEDS or 5-10% DEXTROSE) STOPPED, INTERRUPTED, OR NOT ABSORBED**

- **PATIENTS ON ORAL DIET MUST HAVE INSULIN INFUSION CEASED IMMEDIATELY IF CONTINOUS CALORIC SOURCE CEASED**

- **INSULIN INFUSION CANNOT BE INCREASED MORE OFTEN THAN 4 HOURLY**

BGL < 2.6 mmol/L
- Minimum insulin infusion 1 units/hr
- Intravenous bolus 25 mL x 50% dextrose
- Review current dextrose infusion, enteral, parenteral nutrition
- Measure BGL every 30 minutes or more frequently if symptomatic until > 4.4 mmol/L

BGL 2.6 - 4.3 mmol/L
- Reduce infusion rate by 2 units/hr
- Review current dextrose infusion, enteral, parenteral nutrition
- Measure BGL every 30 minutes or more frequently if symptomatic until > 4.4 mmol/L
- Minimum insulin rate 1 units/hr

BGL 4.4 - 7.0 mmol/L
- If BGL decreased >2 mmol/L in last 4 hrs reduce infusion rate by 1 units/hr
- If BGL decreased ≤2 mmol/L or increased in last 4 hrs continue insulin infusion at existing rate
- Measure BGL 2-hourly x 2, then 4-hourly until BGL leaves target range (4.4-7.0 mmol/L)
- Minimum insulin rate 1 units/hr

BGL 7.1 - 10 mmol/L
- Insulin rate cannot be increased more often than 4-hourly
- If first BGL start at 2 unit/hr
- If BGL decreased > 2 mmol/L in last 4 hr continue insulin infusion at existing rate
- If BGL decreased ≤ 2 mmol/L or increased in last 4 hr increase insulin infusion rate by 1 unit/hr
- Measure BGL at 2-hourly (to detect rapid decrease in BGL)

BGL > 10 mmol/L
- Insulin rate cannot be increased more often than 4-hourly
- If first BGL start at 3 unit/hr
- If BGL decreased > 2 mmol/L, continue insulin infusion at existing rate.
- If BGL decreased ≤ 2 mmol/L or increased, increase insulin infusion rate by 2 unit/hr
- Measure BGL at 4-hourly

APPENDIX 3

BLOOD GLUCOSE CONTROL – SUGGESTIONS FOR TRANSITION TO ORAL DIET

NON-DIABETIC PATENTS
- Cease insulin infusion when caloric infusion (enteral feed, parenteral nutrition, IV dextrose) ceased
- If oral diet re-commenced monitor BGL 4-6/24hrly
- If oral diet not re-commenced consider re-start IV dextrose and monitor BGL 4-6/24 hrly

NON-INSULIN DEPENDENT DIABETIC PATIENTS
- NIDDM patients may require period of s/c insulin to maintain blood glucose control following surgery or critical illness
- Cease insulin infusion when caloric infusion (enteral feed, parenteral nutrition, IV dextrose) ceased
- If tolerating oral diet
  - Diabetic diet
  - Re-commence oral hypoglycaemics
  - Monitor BGL's 4-6/24 hrly
  - Calculating s/c insulin dosage *Example*
    - Add up previous 24hrs total insulin usage *60 units*
    - Calculate 2/3 of this dose *40 units*
    - Give as 4 divided doses daily;
      - 3 doses actrapid s/c with meals *10 units tds*
      - 1 dose protaphane s/c at night *10 units nocte*
  - Review dose requirements daily
  - If BGL control difficult seek Endocrinology review
  - DO NOT RE-START INSULIN INFUSION UNLESS CALORIC INFUSION RE-STARTED
- If not tolerating oral diet
  - Monitor BGL's 4-6/24 hrly
  - Consider IV dextrose infusion until oral diet re-commenced
  - DO NOT RE-START INSULIN INFUSION UNLESS CALORIC INFUSION RE-STARTED

INSULIN-DEPENDENT DIABETICS
- Cease insulin infusion when caloric infusion (enteral feed, TPN, IV dextrose) ceased
- If tolerating oral diet
  - Diabetic diet
  - Recommence regular insulin
  - Monitor BGL's 4 to 6-hourly
  - If BGL control difficult seek Endocrinology review
  - DO NOT RE-START INSULIN INFUSION UNLESS CALORIC INFUSION RE-STARTED
- If not tolerating oral diet
  - Monitor BGL's 4 to 6-hourly
  - Consider intravenous dextrose infusion until oral diet recommenced
  - DO NOT RE-START INSULIN INFUSION UNLESS CALORIC INFUSION RE-STARTED