A phase II randomised controlled trial of intensive insulin therapy in general intensive care patients

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Hyperglycaemia is a common finding in acutely ill patients[1,2] and is frequently associated with an adverse outcome.[1-5] Despite these observations, the concept of normalising blood glucose concentrations in critically ill patients has not been widely adopted for fear of inducing hypoglycaemia.[6,7] However, a large, single-centre, randomised controlled trial[8] found that an intensive insulin regimen maintaining a blood glucose concentration of 4.4–6.1 mmol/L significantly decreased hospital morbidity and mortality in ventilated surgical intensive care patients. Several limitations in this study make the external validity and applicability of the intensive insulin regimen to general intensive care patients uncertain.[9] This uncertainty has been further increased by a similar study in medical intensive care unit patients,[10] which failed to find a reduction in hospital mortality in the intention-to-treat analysis. This has limited uptake of intensive insulin regimens[7,11] and led to numerous calls for large-scale, multicentre trials to resolve the uncertainty.[9,12,13]

In March 2002, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) decided to conduct a large, multicentre, randomised controlled trial (Normoglycaemia in Intensive Care Evaluation [NICE])[14] to determine whether maintaining normoglycaemia (blood glucose concentration, 4.5–6.0 mmol/L) reduces 90-day all-cause mortality in general intensive care patients whose ICU stay was expected to extend to at least a third calendar day. An important aspect of developing the NICE protocol was to determine the safety and effectiveness of an intensive insulin regimen in general intensive care patients who did not receive large amounts of intravenous glucose. Thus, a phase II, randomised controlled study was performed to compare an intensive insulin regimen with a conventional insulin regimen.

Methods

Patients aged 18 years or older who had been admitted to the closed, general ICU of a university-affiliated tertiary hospital, and who were predicted at the time of ICU admission to stay more than 48 hours in the ICU, were eligible for the study. The study period was 1 March to 31 December 2003.

The study protocol was approved by the Australian Capital Territory Health Research Ethics Committee, and

ABSTRACT

Objective: To determine the safety and efficacy of an intensive insulin regimen compared with a conventional insulin regimen in general intensive care unit patients.

Methods: A phase II, randomised controlled trial was conducted in 70 critically ill patients in a closed multidisciplinary ICU of a university-affiliated tertiary hospital. We assessed patient characteristics at baseline. Trial process measures included number of blood glucose measurements per day and number in target range, type and quantity of caloric intake, patient outcome and insulin dosing. The primary outcome was the median blood glucose concentration. Secondary outcome measures were incidence of hypoglycaemia (blood glucose level < 2.2 mmol/L), clinical sequelae of hypoglycaemia and hospital mortality.

Results: Thirty-five patients were randomised to each of the two groups. More blood glucose samples were taken per day in the intensive insulin group (16 versus 9), but the number of samples in the normoglycaemic range was 48.5%, compared with 79.8% within the target glucose range in the conventional insulin group. The median (interquartile range) blood glucose concentrations in the intensive and conventional insulin therapy groups were 5.4 (5.1–5.7) mmol/L and 7.9 (7.2–9.0) mmol/L, respectively (difference, 2.5 mmol/L; $P < 0.0001$). Five patients (14.3%) in the intensive insulin therapy group became hypoglycaemic versus none in the conventional insulin therapy group. There were no detected clinical sequelae of hypoglycaemia.

Conclusion: The intensive insulin regimen was effective in achieving the target blood glucose concentration, with clear separation from the conventional insulin regimen. Although the incidence of hypoglycaemia was increased, there was no detectable harm.

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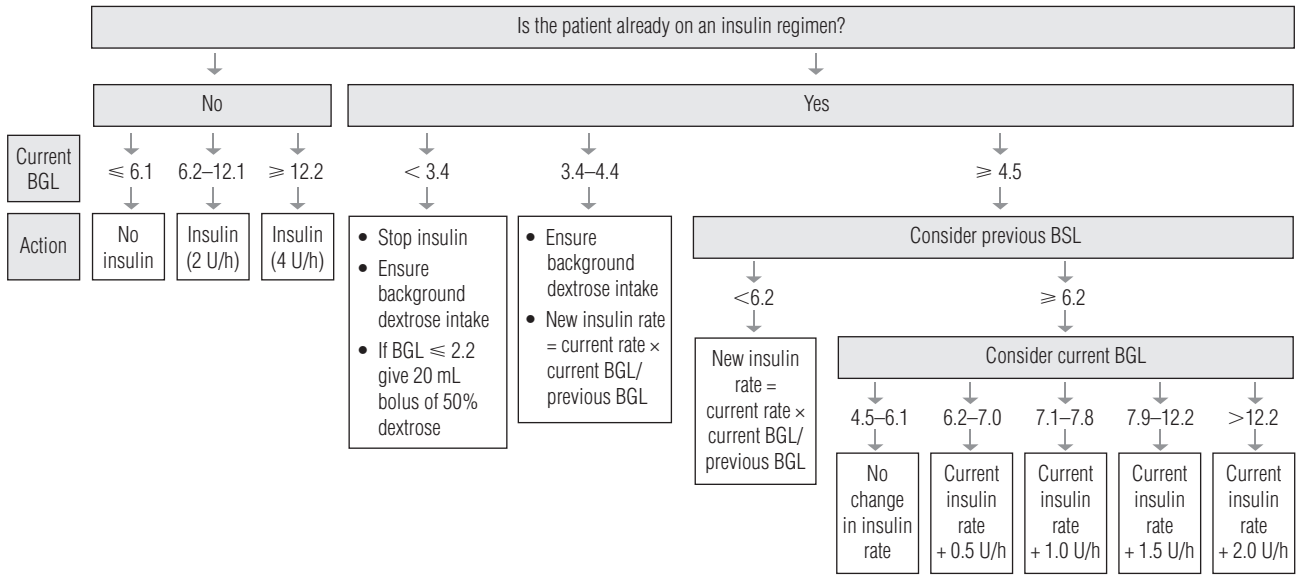
Figure 1. Algorithm for intensive insulin regimen



BGL = blood glucose level (mmol/L). ◆

Figure 2. Algorithm for conventional insulin regimen

BGL (mmol/L)	Insulin infusion (U/h)	Comments
Initial measure	0	
> 12.0	1	Starting rate
> 11.1	Up 1	Increase insulin each hour until BGL < 11.1 mmol/L
9.99–11.1	Steady as is	
< 9.99	Down	Stop if fall continues Resume only when BGL > 12.0

BGL = blood glucose level (mmol/L). ◆

informed consent was obtained from each patient or their legal surrogate.

Eligible patients were randomly allocated to receive either an intensive or a conventional insulin regimen. Patients were assigned to treatment group by means of sealed, opaque envelopes balanced with permuted blocks of 10. Blinding of the medical and nursing staff to the insulin regimen was not possible.

In the intensive insulin regimen group, an insulin infusion (50 IU Actrapid HM [Novo Nordisk, Copenhagen, Denmark] in 50 mL 0.9% sodium chloride) was commenced if the blood glucose concentration exceeded 6.1 mmol/L, and was then titrated to maintain the blood glucose concentration at 4.4–6.1 mmol/L according to an algorithm (Figure 1). In the conventional insulin regimen group, an insulin infusion was commenced if the blood glucose concentration exceeded 12 mmol/L, and was then titrated to maintain a blood glucose concentration at 10–11.1 mmol/L according to an algorithm (Figure 2).

The two insulin algorithms were modified from those used by Van den Berghe and colleagues in their first study.[8] Education sessions were conducted before the trial to facilitate the safe introduction of the two algorithms into the ICU.

The insulin infusion rate was adjusted by the bedside ICU nurse using the appropriate algorithm, based on measurements of whole-blood glucose in undiluted arterial blood. These were initially performed at hourly intervals using a glucose analyser (Rapidlab 864, Bayer HealthCare, Bayer Australia). Once a steady glucose state was achieved, frequency was reduced (minimum, 4-hourly). The insulin protocols were used only in the ICU; management of blood glucose after ICU discharge was at the discretion of the patient's treating specialist.

Enteral feeding was initiated as soon as practical in all patients and standardised according to local unit guidelines; it was not routine practice to use interim parenteral nutrition or large doses of intravenous glucose. All other aspects of intensive care management were left to the discretion of the treating intensive care specialists.

Data collection and outcome measures

Baseline data included demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) II score,[15] diagnosis and blood glucose concentration on admission, and presence of pre-existing diabetes mellitus. After patients

Table 1. Baseline characteristics of patients in the trial, by type of insulin regimen

Variable	Intensive regimen ($n = 35$)	Conventional regimen ($n = 35$)
Median age (years) (IQR)	66.28 (59.5–74.9)	64.6 (57.7–73.1)
Sex	22 M, 13 F	20 M, 15 F
Median BMI (kg/m^2) (IQR)	26.1 (23.5–28.9)	23.9 (21.2–26.1)*
Median APACHE II score (IQR)	19 (16–23)	22 (20–29)*
ICU admission source		
Operating theatre	8	8
Emergency department	10	13
Ward	7	7
Other hospital	10	7
Type of admission		
Medical	23	20
Elective surgery	2	1
Emergency surgery	10	14
Diagnostic group		
Cardiovascular	7	10
Respiratory	11	8
Gastrointestinal	3	7
Neurological	3	5
Sepsis	4	1
Trauma	6	4
Renal	1	0
Past history of diabetes	6	4
Diet-controlled	0/6	2/4
Oral hypoglycaemics	4/6	1/4
Insulin	2/6	1/4
Median days of stay (IQR)		
ICU	5 (3–8)	4 (3–9)
Hospital	15 (7.5–28.5)	18 (11–31.5)

IQR = interquartile range. BMI = body mass index.
* $P < 0.01$ for difference between insulin regimens. ◆

were allocated to groups, blood glucose measurements, hourly insulin dosing, and type and quantity of caloric intake were recorded until ICU discharge or death.

The primary outcome measure was the median blood glucose concentration. Secondary outcome measures were the incidence of hypoglycaemia (blood glucose concentration < 2.2 mmol/L), and ICU and hospital mortality.

Statistical analysis

Using data from Van den Berghe et al's first study and the standard sample size formula,[16] a minimum of 31 patients per group (62 patients total) were required to detect a difference of two standard deviations of overall mean blood glucose concentration between the two groups with 95% certainty at 80% power. Target recruitment was set at 35 patients per group.

Numerical data are presented as median and interquartile range (IQR). Categorical data are presented as counts and percentages. Data were analysed using S-PLUS 6.1 for Windows (Insightful Corporation, Seattle, USA). Differences between groups were assessed using *z* tests for numerical data and χ^2 tests for categorical data.

The median glucose concentration was calculated for each patient and, using these data, for each treatment regimen.

Results

Of the 264 eligible patients, 70 were enrolled (35 in each group). Reasons for exclusion included failure to gain consent and failure to capture patients outside normal working hours. The 70 enrolled patients comprised both medical patients (43/70, 61%) and surgical — mostly emergency — patients (27/70, 39%). The median age was 65.8 years (IQR, 59–74.6 years), and patients were predominantly male (42/70, 60%). Baseline characteristics were similar between the two groups, with some important differences, including a lower admission APACHE II score, a greater number of patients being admitted with sepsis and a higher body mass index in patients randomised to the intensive insulin regimen group (Table 1).

Blood glucose control

In the intensive insulin group, all patients received intravenous insulin at some time during their ICU stay. They averaged 16 measurements of glucose per day and achieved a median blood glucose concentration of 5.4 (IQR, 5.1–5.7) mmol/L. Almost half the glucose measurements (48.5%; 1655/3411) were in the range 4.4–6.1 mmol/L. The insulin algorithm was followed for 55.5% of the hours of the trial (Table 2).

In the conventional insulin group, 17 patients (49%) received intravenous insulin, achieving a median blood glucose concentration of 7.9 (IQR, 7.2–9.0) mmol/L with an average of nine glucose measurements per day. Most glucose measurements (79.8%; 2301/2882) were in the range 4.1–11.0 mmol/L, and the insulin algorithm was followed for 78.5% of the hours of the trial (Table 2).

Hypoglycaemia

Hypoglycaemia (blood glucose < 2.2 mmol/L) was recorded in eight blood samples (8/3411; 0.23%) from five patients (14.3%) in the intensive insulin group, with no associated patient compromise or detectable clinical sequelae. There were no incidents of hypoglycaemia in the conventional insulin group.

Table 2. Glucose control, by type of insulin regimen*

Variable	Intensive regimen	Conventional regimen
Time to randomisation from ICU admission (h)	11.7 (5.4–19.8)	12 (4.9–17.2)
Admission BGL (mmol/L)	7.6 (6.5–8.5)	7.8 (6.9–10.9)
Time to target BGL from randomisation (h)	4 (1.5–6.5)	11 (3.3–20.8)†
Median hourly BGL for each patient (mmol/L)	5.4 (5.1–5.7)	7.9 (7.2–9.0)‡
Median hourly insulin dose (IU)	2.3 (1–3.4)	0 (0–3)‡
Median daily insulin dose (IU)	35.7 (19.2–70.2)	0 (0–6)‡
Number of blood samples in target range	1655/3411 (48.5%)	2301/2882 (79.8%)
Number of patients hypoglycaemic (< 2.2 mmol/L)	5 (14.3%)	0
Number of blood samples hypoglycaemic (< 2.2 mmol/L)	8/3411 (0.23%)	0/2882
Median daily intravenous dextrose (g)	12.5 (0–26)	1.5 (0–10.5)
Median daily enteral feed (kcal)	720 (0–1480)	830 (0–1575)
Correct dose of insulin administered	2524/4548 (55.5%)	4923/6275 (78.5%)
Daily median number of glucose samples	16 (8–22.3)	9 (5–12)‡

BGL = blood glucose level. * Figures are group median (interquartile range) unless otherwise indicated. † $P < 0.001$. ‡ $P < 0.0001$. ◆

Mortality

Seven patients in the intensive insulin group (20%) died during intensive care, compared with two patients in the conventional insulin group (6%) ($P = 0.15$). A further two patients in the intensive insulin group died before hospital discharge (26% hospital mortality) and a further one patient in the conventional insulin group (9% hospital mortality) (absolute difference, 17%; $P = 0.11$; relative risk, 3.0 [95% CI, 0.78–15.69]). The most common cause of death in the intensive insulin group was sepsis with multi-organ failure (Table 3).

Discussion

The two insulin regimens used in this study produced a clear separation in median blood glucose concentrations, with concentrations similar to or lower than those reached in Van den Berghe et al's first study.[8] However, in the intensive insulin group, only 48.5% of the samples were within target range, with 55.5% compliance with the insulin algorithm. Other studies have found that reasons for limited compliance include failure to interpret the complex algorithm,[17] fear of inducing hypoglycaemia,[7] failure to operate the algorithm because of excessive workload,[18] and failure of the insulin algorithm to cater for individual differences in insulin dose responsiveness.[3] Previous reports suggest that a bedside computerised algorithm may increase the percentage of time the blood glucose concentration is within the target range and reduce the incidence of hypoglycaemia.[17,19]

Other studies reviewing tight glycaemic control have reported similar numbers of samples with glucose concentration outside the target range.[11,17,19-21] The importance of consistently staying within the target range remains unclear, given that the studies reporting a positive benefit have not commented on time spent within the target range.[8] There does appear to be a relationship between the morning blood glucose concentration and subsequent glucose control.[19] Equally, there is also no agreement on which glucose target confers the maximum benefit to patients while minimising the risk of hypoglycaemia.

The greatest concern with employing an intensive insulin regimen in general intensive care patients without significant use of parenteral nutrition or supplemental intravenous glucose is the incidence of severe hypoglycaemia. In

Table 3: Mortality, by type of insulin regimen

Variable	Intensive regimen	Conventional regimen
Mortality		
Intensive care unit	7/35 (20%)	2/35 (6%)
Hospital	9/35 (26%)	3/35 (9%)
Cause of death		
Acquired immunodeficiency syndrome	0	1
Sepsis with multi-organ failure	4	0
Ruptured abdominal aortic aneurysm with multi-organ failure	1	0
Hypoxic respiratory failure		
Vasculitis	0	1
Pulmonary fibrosis	1	0
Traumatic brain injury	1	0
Hypoxic brain injury	0	1
Metastatic cancer	2	0

our study, there was an increase in the number of patients suffering a severe hypoglycaemic event (5/35, 14.3%) although this was only 0.23% (8/3411) of the blood samples taken, and no clinically significant sequelae were detected. The incidence of severe hypoglycaemia in our study is similar to that seen in other studies.[8,11,17,19,22] The incidence varies from 0.34%[9] to 42%[12] of patients and depends on the target glucose range and the definition of severe hypoglycaemia used.

The major strengths of this trial are that there was effective concealment of allocation for randomisation, and that intention-to-treat analysis was performed. A potential shortcoming was that the two insulin regimens could not be blinded, but to date no investigator has been able to do this. Over the 10 months of the trial, 26.5% (70/264) of eligible patients were randomised, which is similar to the proportion reported by other groups.

As expected in a study of this size, the two groups were not evenly matched at baseline, and this possibly influenced results. However, the trial was designed to study the biochemical effect of the two glycaemic control regimens rather than their clinical effect. In a study of this size, differences in mortality rates are highly likely to have arisen by chance.

Conclusion

The two insulin regimens used in this study provided a clear separation in median blood glucose concentration. In the intensive insulin group there was an increase in the incidence of hypoglycaemia, without detectable harm. The rate of failure to comply with the bedside insulin algorithm has led to the development of a web-based algorithm for the NICE-SUGAR trial.[23] This facilitates close monitoring of glycaemic control and hypoglycaemic events.

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