

Introduction of intensive glycaemic control into a neurosurgical intensive care unit: a retrospective cohort study

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Hyperglycaemia and insulin resistance are common in critically ill patients and have been reported to increase the rate of complications. Hyperglycaemia is a poor prognostic indicator in patients with ischaemic stroke, cerebral haemorrhage and subarachnoid haemorrhage,¹ as well as traumatic brain injury.²⁻⁴ However, there is little evidence regarding the possible benefits of improved glucose control on outcome in these patients.

A prospective randomised controlled trial by Van den Berghe and colleagues showed that an intensive insulin protocol targeting blood glucose to low-normal levels (4.4–6.1 mmol/L) was associated with reduced morbidity and mortality in the surgical intensive care unit.⁵ It is debated whether the benefits arose from the avoidance of hyperglycaemia, the administration of insulin, or both.⁶ Subgroup analysis of neurological outcomes in the patients admitted for at least 7 days showed that intensive insulin therapy reduced intracranial pressure and the need for inotropes and vasopressors, while seizures and diabetes insipidus occurred less often.² These results complement other reports suggesting that hyperglycaemia is associated with worse clinical outcomes. Traumatic brain injury can itself induce hyperglycaemia, which is compounded by exogenous and iatrogenic variables.⁶

The widespread impact of the trial by Van den Berghe et al⁵ was felt in our own ICU, where individual clinicians perhaps informally began to target lower blood glucose levels more actively, resulting in a fall in mean blood glucose level (BGL) from 9.5 mmol/L to 8.5 mmol/L after the trial was published.⁷ In July 2003, we formally introduced an intensive insulin protocol into the neurosurgical ICU. To date, we do not know of any published literature specifically examining the effect of intensive insulin therapy on neurosurgical patients, or evidence to suggest that it is effective or of benefit in this subgroup.

The aim of this retrospective study is to describe the BGL outcomes in the year before, and the year after, the introduction of the intensive insulin protocol into our neurosurgical ICU.

Methods

The study was conducted in the Neurosurgical Intensive Care Unit of Royal Prince Alfred Hospital, Sydney, New

ABSTRACT

Background: There is evidence that intensive glycaemic control decreases morbidity and mortality in surgical intensive care unit patients. In traumatic brain injury, hyperglycaemia is a prognostic indicator.

Objective and study design: This retrospective cohort study describes the blood glucose level outcomes before and after the introduction of an intensive insulin protocol to a neurosurgical ICU.

Methods: We analysed data on all patients admitted to a neurosurgical ICU during the year before, and the year after, the introduction in July 2003 of an intensive insulin protocol targeting patient blood glucose level (BGL) to 4.4–6.1 mmol/L. Patients who underwent fewer than 20 BGL measurements during the ICU admission were excluded. Data were obtained from an electronic clinical information system.

Results: 121 patients were enrolled: 64 before and 57 after introduction of the protocol. The groups were similar in sex, age, and severity of illness on ICU admission. After introduction of the protocol, BGL was significantly lower (weighted mean BGL, 6.73 mmol/L v 7.77 mmol/L before; $P < 0.001$), and proportion of BGL readings in the target range was greater (37% v 21% before; $P < 0.001$). In addition, BGL variability was greater (weighted mean standard deviation, 2.03 v 1.88 before; $P < 0.001$), hypoglycaemia was more common (0.58% of BGL readings v 0.20% before; $P = 0.06$), and ICU stay was significantly longer, but there was no difference in median Glasgow Coma Scale score or ICU discharge status (alive or dead).

Conclusions: The intensive insulin protocol was effective in lowering blood glucose in neurosurgical ICU patients.

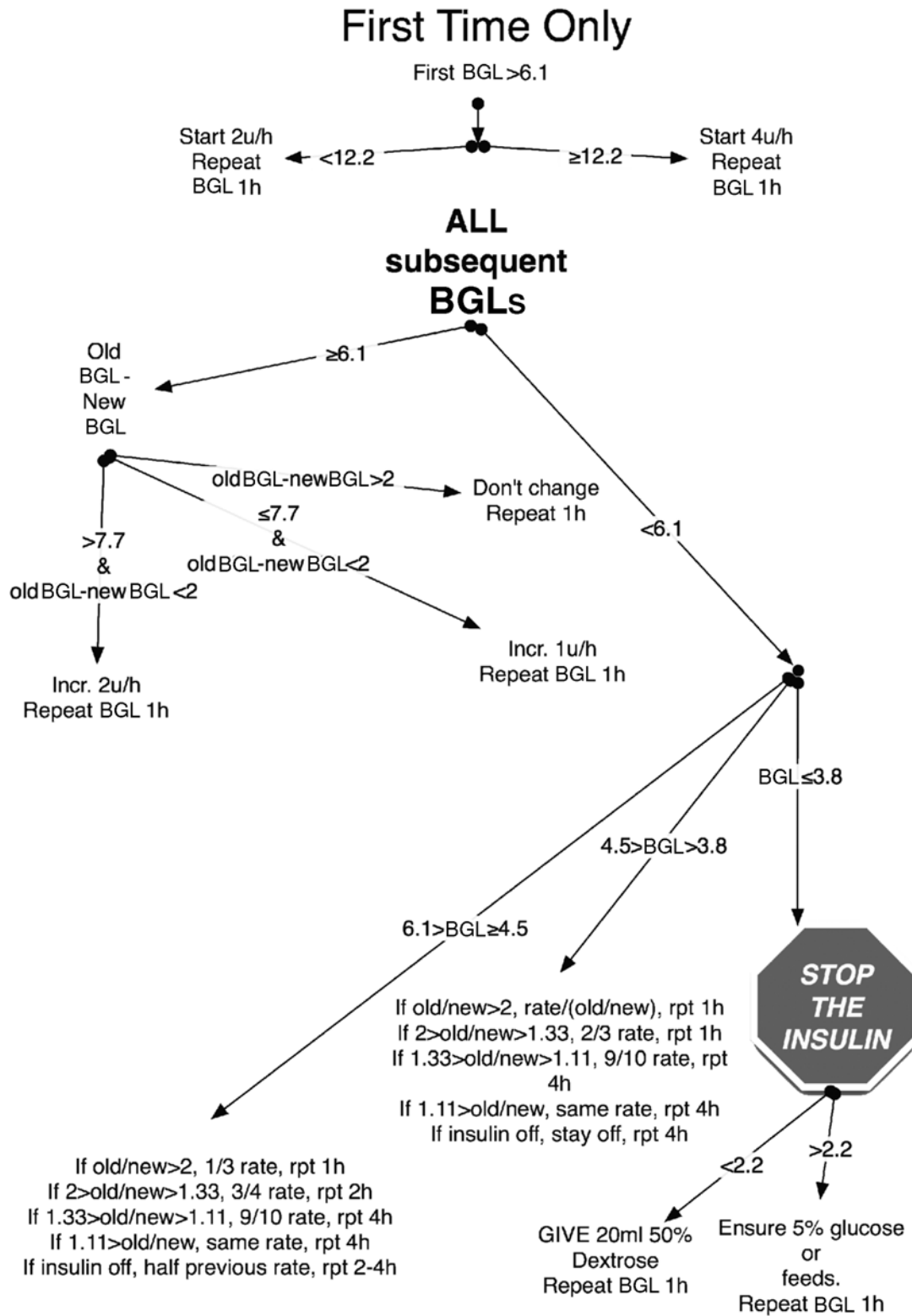
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South Wales. The ICU has 10 beds, comprising both intensive care and high dependency beds. The study was approved by the institutional research ethics committee.

Patient group

The intensive insulin protocol was introduced to the ICU on 31 July 2003. All patients admitted to the unit between

Figure 1. Intensive insulin protocol used in the Neurosurgical Intensive Care Unit, Royal Prince Alfred Hospital, Sydney, New South Wales



BGL = blood glucose level (mmol/L).

00:01 on 31 July 2002 and 23:59 on 31 July 2004 were included in the analysis. Patients with fewer than 20 BGL readings during the admission were excluded, on the basis that they had been inadequately exposed to clinical management of BGL in the ICU.

Intensive insulin therapy

Before the introduction of the intensive insulin protocol, intravenous insulin infusion was initiated if BGL exceeded 12 mmol/L. Dosages were adjusted to maintain BGL between 10 and 11 mmol/L, and tapered if BGL fell below 10 mmol/L.

The intensive insulin protocol is outlined in Figure 1. A continuous insulin infusion (Actrapid HM [Novo Nordisk], 50 units in 50 mL of 5% dextrose) was initiated if BGL exceeded 6.1 mmol/L. After the protocol was begun, if BGL still exceeded 6.1 mmol/L, then the infusion rate was steadily increased until the normoglycaemic range was reached (4.4–6.1 mmol/L). In the maintenance phase, small adjustments were made to the infusion rate, unless BGL was more than 6.1 mmol/L, in which case the stabilisation phase was recommenced, or unless BGL was less than 3.8 mmol/L, in which case insulin was stopped, and intravenous dextrose was given. Insulin was also stopped if enteral feeding or intravenous administration of dextrose was ceased, or if the patient was transferred from the unit.

Data collection

Our unit uses a clinical information system (CareVue, Philips Electronics, Eindhoven, Netherlands) to electronically record patient data at the bedside. BGLs were measured by bedside glucometers and by arterial blood sampling. Glucometer results are manually entered into the CareVue vital signs flowsheet; BGLs from arterial blood samples are transferred automatically from the hospital pathology system.

The database was queried by one investigator (AR) to obtain a dataset for each patient. This comprised all BGL measurements, along with temperature, length of stay in the ICU and score on the Glasgow Coma Scale (GCS). Using the medical record number, we also obtained demographic data for each patient from the hospital database, including age on admission, sex and diagnosis.

Statistical analysis

Statistical analyses were carried out using SPSS version 14.0 (SPSS Inc, Chicago, Ill, USA). The mean values of continuous variables in each group were compared using a *t* test for independent samples. The standard deviation of an individual's BGL readings was selected as the best summary measure of BGL variability, according to the principles described by Matthews et al.⁸ The number of

Table 1. Baseline characteristics of patient groups before and after introduction of the protocol

	Before	After
Number of patients	64	57
Male sex: no. (%)	35 (55%)	33 (58%)
Mean age in years (95% CI)	54.8 (50.7–59.0)	51.0 (46.0–56.0)
Mean APACHE II score (95% CI)	19.4 (17.6–21.2)	20.0 (17.6–22.3)
Median GCS on admission (IQR)	7 (4–13)	5 (3–12)

GCS = Glasgow Coma Scale score. IQR = interquartile range.

Table 2. Comparison of unweighted and weighted individual patient mean BGL and BGL variability (SD), before and after introduction of the protocol

	Before	After	<i>P</i>
Unweighted analysis			
Mean BGL (mmol/L) (SD)	7.88 (1.40)	7.06 (1.94)	0.008
Mean SD of an individual's BGLs (SD)	1.97 (0.91)	2.16 (1.16)	0.33
Weighted analysis*			
Mean BGL (mmol/L) (SD)	7.77 (1.27)	6.73 (1.56)	<0.001
Mean SD of an individual's BGLs (SD)	1.88 (0.76)	2.03 (1.11)	<0.001

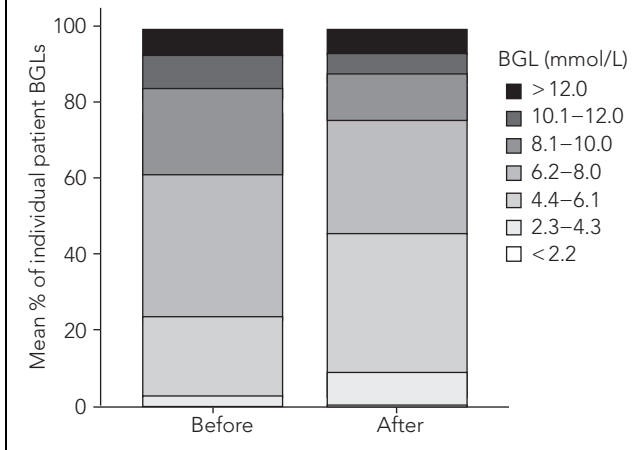
BGL = blood glucose level. * Weighting is by the number of BGL measurements undertaken in that patient.

BGL measurements performed on an individual is a surrogate measure of exposure to the insulin protocol, both in terms of length of ICU stay, and frequency of BGL measurement. As some individuals contributed more to the data than others, our study design was clustered.⁹ Therefore, we also compared BGL mean and variability after weighting by the number of BGL measurements.¹⁰ The number of BGL readings per patient, and the median GCS score at ICU discharge were compared using the Mann–Whitney U test; the distribution of both variables was markedly skewed. ICU discharge status (dead or alive) was compared using the χ^2 test.

Results

Of the 568 patients admitted to the neurosurgical ICU during the study period, 121 were enrolled in the study (64 before, and 57 after, introduction of the intensive insulin protocol). The patient groups before and after the protocol were similar with respect to sex, age, and severity of illness

Figure 2. Mean distribution of blood glucose (BGL) results before and after introduction of the protocol



on admission to the ICU (Table 1). Although GCS score on admission was higher before the introduction of the protocol (7 v 5; Table 1), the difference was not statistically significant ($P=0.18$).

We analysed 11 326 BGL measurements (a patient who underwent 770 BGL measurements was excluded as an outlier). The median number of BGL measurements per patient was 70 (interquartile range [IQR], 37–127). The median number of BGL readings per patient before the protocol was 53 (IQR, 35–115) and after the protocol was 82 (IQR, 37–132) ($P=0.51$).

The intensive insulin protocol was associated with a very significant overall reduction in BGL (Table 2). Individual patient (unweighted) mean BGL was reduced from 7.88 to 7.06 mmol/L ($P=0.008$). The BGL-lowering effect of the insulin protocol increased when we weighted the individual patient mean BGL results by the number of readings. The weighted individual patient mean BGL fell from 7.77 to 6.73 mmol/L after the protocol ($P<0.001$). BGL variability was significantly greater after the introduction of the protocol in the weighted analysis (mean standard deviation, 1.88 before v 2.03 after; $P<0.001$) (Table 2).

The BGL-lowering effect of the insulin protocol is detailed in Figures 2 and 3. There was a substantial increase in the proportion of BGL readings in the therapeutic target range of 4.4–6.1 mmol/L. The average percentage of an individual's total BGL readings in this range increased from 21% to 37% ($P<0.001$) (Figure 3A), which was the largest single change among seven clinical ranges of BGL. The incidence of serious hypoglycaemia (<2.2 mmol/L) was low in both groups in absolute terms, with a borderline significant increase after introduction of the protocol (0.20% of BGL readings before v 0.58% after, $P=0.06$) (Figure 3B).

Figure 3. Mean percentage of patient blood glucose (BGL) results in two clinically relevant ranges before and after introduction of the protocol

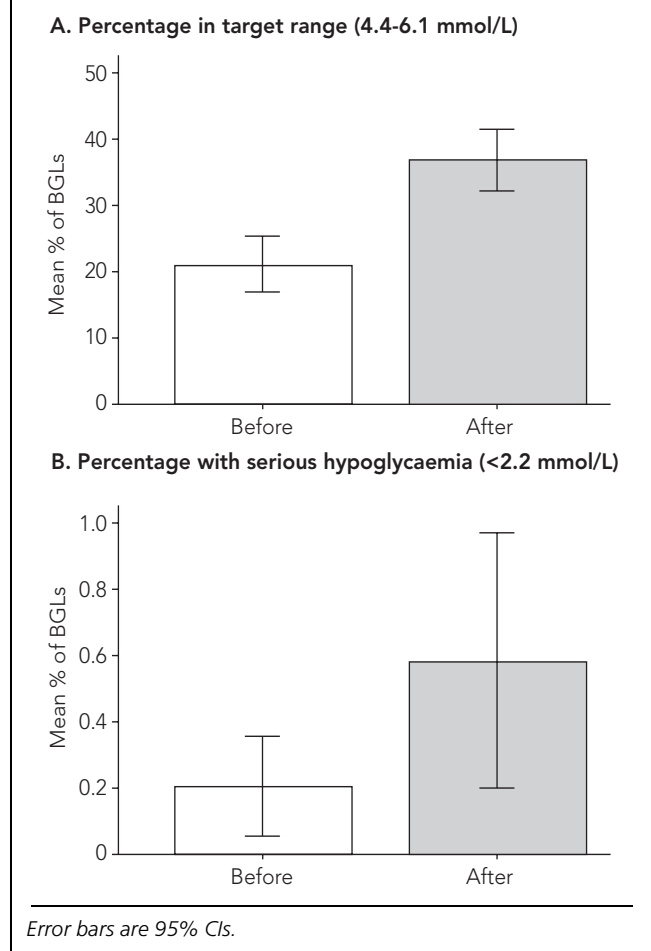


Table 3. Comparison of clinically relevant outcomes before and after introduction of the protocol

	Before	After	P
Mean length of ICU stay (days)	12.7	17.9	0.03
Median GCS at discharge from ICU	11	10	0.26
ICU discharge status: no. alive (%)	53 (84%)	46 (84%)	0.94

GCS = Glasgow Coma Scale score.

Table 3 shows the univariate comparison of clinical outcomes. Mean length of stay in the ICU was significantly longer during the year after introduction of intensive glycaemic control (17.9 v 12.7 days, $P=0.03$). We observed no significant differences in median GCS at ICU discharge or ICU discharge status (dead or alive).

Discussion

This study showed that the intensive insulin protocol was effective at achieving the intended BGL outcomes in a neurosurgical intensive care population. BGL was significantly lower after the introduction of the protocol, an effect that was more marked when weighted by individual exposure to BGL management in the ICU (by total number of BGL readings). The clinical importance of the increase in serious hypoglycaemia is unknown, but we are reassured that our protocol is safe: the incidence of serious hypoglycaemia after the introduction of the protocol remained low in absolute terms (0.58% of all BGL readings per patient). To our knowledge, this is the first study that specifically addresses whether this intervention is appropriate in neurosurgical intensive care patients.

The variability in BGL in the weighted analysis was greater after the introduction of the protocol. The reasons are unclear, but it might be that the protocol was attempting to maintain BGL in a narrow range below the homeostatic level for most of our patients. It might also reflect our lack of experience using the protocol in its first year of introduction. Responsiveness to the extra work imposed by the protocol, particularly by nursing staff, was an important factor in determining its likely success. We were surprised, therefore, to observe no significant difference in the median number of BGL readings in the period after its introduction. This might be explained by the exclusion at the design stage of all patients who underwent fewer than 20 BGL measurements, which biased our ability to measure the true impact of the protocol in terms of nursing intervention at the bedside for all patients admitted to the ICU.

Length of stay in the ICU was increased in the protocol group. It is outside the scope of this study to examine the reasons for this, but they may relate to non-clinical factors, and we postulate that an increase in exit block from the ICU to ward areas of the hospital occurred during the course of the study.

The principal strength of this study is our use of an electronic clinical information system to capture, store, and analyse all BGL measurements in a large neurosurgical ICU over a 2-year period. The link to the hospital pathology and demographic systems also allowed us to accurately characterise the patient groups, and measure some confounding variables. These results are the first that can be applied to the neurosurgical critical care population and provide reassurance that intensive insulin control is safe in this vulnerable population. The insulin protocol that we adopted is also effective at achieving the desired BGL outcomes. Use of the protocol by the nursing staff at the bedside is assisted by a simple software program of our own design, which pro-

vides clinical instructions according to Figure 1 in response to manual entry of BGL readings into the bedside computer.

This study is limited by the fact that it is a retrospective cohort study. It was not feasible to prospectively randomise patients to two different insulin protocols. Treatment of hyperglycaemia in the period before introduction of the protocol was not strictly standardised, and no adjustment was made for exogenous factors, such as caloric intake, catecholamine administration or diabetes status. Our baseline matching between groups, and clinical outcome variables were relatively basic. Groups were evenly matched in terms of sex, age and APACHE II scores. Because of these limitations and the small sample size, we did not consider that a multivariate analysis of the clinically relevant outcomes would be valid.

Although the study defined a cut-off date at which the protocol was introduced, the process was probably more gradual, allowing for staff education and familiarisation with the protocol. This may have resulted in non-compliance to the protocol, particularly during the early stages of its implementation.

These data add to a growing body of literature concerning glycaemic control during critical illness. We believe they are an important addition for the neurosurgical subgroup, which might reasonably be expected to differ from a general ICU population. Some other data have been obtained on glycaemic control in a neurosurgical population. The UK Glucose Insulin in Stroke Trial (GIST-UK) revealed that glucose-potassium-insulin infusions decrease plasma glucose concentrations in patients with acute stroke, but this was not associated with any beneficial clinical outcome.¹¹ An observational study of 338 patients with traumatic brain injury found a linear relationship between hyperglycaemia in the first 24 hours after the injury and mortality, suggesting that BGL might also be an indicator of injury severity.¹² A prospective study of 267 patients with moderate and severe head injury found that admission and postoperative BGLs were independent predictors of injury severity and outcome.¹³

Conclusions

We have demonstrated the effective application of an intensive insulin control protocol to a neurosurgical ICU population. We used an electronic clinical information system to capture and analyse all BGL data over a 2-year period, but the method limited our ability to investigate the effect of many covariables. These results offer some support for continuing our practice of intensive insulin control in this discrete population, at least until results of large multicentre trials of intensive insulin therapy become available.¹⁴

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MDW led the study and drafted the manuscript; DJG performed the data analysis and drafted the manuscript; AR maintained the database and extracted the data; and RT wrote the local protocol. All authors read and approved the final manuscript.

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