

Enteral nutrition versus glucose-based or lipid-based parenteral nutrition and tight glycaemic control in critically ill patients

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Recent clinical research in intensive care units has shown that early administration of adequate nutritional support and attention to tight glycaemic control are each associated with reductions in morbidity and mortality in critically ill patients.¹⁻⁵ Although apparently independent findings, there is an inevitable physiological link between the administration of nutritional substrates and blood glucose levels and their control with exogenous insulin. Generally accepted best practice considers enteral nutrition (EN) superior to parenteral nutrition (PN), and mandates that EN be commenced in preference to PN when artificial nutrition is prescribed.⁶

However, EN can be difficult to establish in patients within the first week of critical illness, principally because of gastrointestinal intolerance or frequent interruptions to feeding.^{7,8} This commonly leads to inadequate caloric intake.⁷⁻⁹ A recent meta-analysis by Simpson and Doig suggested that early use of PN may result in reduced mortality compared with delayed (> 24 hours) administration of EN.¹⁰ Tight glycaemic control strategies emphasise attention to nutrition, but there has been no systematic analysis of the impact of nutrition strategies on glucose control.

Hyperglycaemia and insulin resistance are common physiological derangements in both diabetic and non-diabetic patients admitted to ICUs,¹¹ and hyperglycaemia may be exacerbated in this patient population by administration of high concentrations of intravenous dextrose.¹² PN solutions traditionally comprise a high-concentration dextrose solution to provide calories combined with an amino-acid solution, infused intravenously continuously over 24 hours. Fat emulsions are administered principally to avoid deficiency of essential fatty acids. Although these emulsions are an efficient source of non-protein calories, many clinicians avoid their continuous administration because of evidence linking their use to immunosuppression and lung injury.¹³ However, others consider these risks to be very low in the clinical setting, especially if modern emulsions are used, and recommend continuous daily infusion of fat as part of a "balanced" PN regimen.¹⁴

We hypothesised that blood glucose control would be better achieved in patients fed EN than PN and, in the latter group, would be better achieved with a "balanced" PN solution than with a dextrose-based PN solution plus twice

ABSTRACT

Objective: Early administration of nutrition and attention to tight glycaemic control are both associated with improved outcomes in critically ill patients. We hypothesised that blood glucose control would be better achieved in patients receiving enteral rather than parenteral nutrition and, in the latter group, would be better achieved using a "balanced" glucose plus lipid solution than a dextrose-based solution as calorie source.

Methods: We conducted a retrospective interrogation of the intensive care database as part of a clinical audit of a 12-bed mixed medical and surgical ICU in a tertiary referral teaching hospital between September 2003 and March 2004. Patients expected to stay in the ICU for longer than 48 hours were treated according to an intensive insulin therapy protocol. They received enteral nutrition (EN) or, if EN was not tolerated, parenteral nutrition (PN) or combined EN and PN. PN comprised a glucose-based solution (GluPN) during the first 3 months of the study and a balanced glucose plus lipid solution (LipPN) during the second 3 months.

Results: 96 patients were treated according to the protocol. Patients receiving PN ($n = 26$) had significantly longer ICU length of stay and greater daily caloric intake than did those receiving EN ($n = 70$) during both study periods. Mean blood glucose, percentage of blood glucose measurements within the target range, and daily insulin dose did not differ significantly between patients receiving EN and PN or GluPN and LipPN.

Conclusion: When used in association with a tight glycaemic control regimen, PN is not associated with poorer glycaemic control in critically ill patients than EN.

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weekly lipid administration. As it had been decided to change from a dextrose-based to a balanced PN solution in our ICU, we took the opportunity to conduct an audit of glycaemic control over 6 months to compare the effect of EN versus PN, and glucose- versus lipid-based PN on the achievement of tight glycaemic control.

Table 1. Clinical characteristics of patients, by audit group (values are mean and SEM unless otherwise stated)

	Glucose-based PN feeding period (Glu)			Lipid-based PN feeding period (Lip)		
	ALL (n=52)	EN (n=41)	PN (n=11)	ALL (n=44)	EN (n=29)	PN (n=15)
Age (years)	55.75 (18.53)	55.59 (19.88)	56.36 (13.03)	61.34 (16.16)	60.59 (15.68)	62.80 (17.52)
Female (%)	32%	27%	50%	32%	24%	47%
APACHE II score	25.73 (9.88)	25.44 (10.60)	26.82 (6.85)	26.89 (9.24)	26.79 (9.71)	27.07 (8.59)
Surgical (%)	44%	38%	70%	55%	52%	60%
Diabetes mellitus (%)	16%	18%	10%	20%	17%	27%
ICU length of stay (days)	8.56 (1.58)	5.28 (0.49)	20.45 (6.01)*	9.40 (1.38)	6.10 (1.06)	15.85 (2.90)*

ALL = all patients during the respective period. EN = enteral nutrition. PN = parenteral nutrition.

* $P < 0.05$ for comparison with ALL or EN for the respective feeding period.

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Methods

Setting and participants

The audit was conducted between September 2003 and March 2004 in a 12-bed general (medical and surgical) ICU in a tertiary referral teaching hospital. During this period, all mechanically ventilated patients expected to remain in the ICU for longer than 48 hours were treated according to an intensive insulin therapy protocol, based on that of Van den Berghe et al,² unless diabetic ketoacidosis or non-ketotic hyperglycaemic coma was the admitting diagnosis.

Blood glucose and nutritional management

If the patient's blood glucose level exceeded 6.1 mmol/L, a continuous infusion of insulin was commenced (50 IU Actrapid HM [Novo Nordisk Pharmaceuticals, Sydney, NSW] in 50 mL 0.9% sodium chloride), and adjusted to maintain blood glucose level in the range 4.4–6.1 mmol/L. Insulin doses were adjusted by the bedside nurse using a computer program which automatically calculated the required insulin infusion rate from the measured blood glucose reading and current insulin dose (Insulin Calculator, R Totaro, Sydney, NSW). A maximum insulin infusion rate of 50 IU/h was permitted.

On ICU admission, all patients were fed continuously with a 25% dextrose solution infused via a central venous catheter at a rate of 36 mL/h, providing 216 g dextrose over 24 hours. This was continued until either enteral feeds were tolerated (60 kcal/h for at least 6 hours) or PN was begun.

On Day 2, EN was commenced unless there was a contraindication to administering nutrition via the gastrointestinal tract, in which case PN was administered. For patients receiving EN, we aimed to provide at least 25 kcal/kg/day of non-protein calories and to reach caloric targets within 48 hours. If the EN rate had not achieved a minimum of 60 kcal/h by 48 hours, then PN was begun. This was

either supplemental (in patients able to tolerate some EN) or total (in patients where EN was ceased).

Enteral nutrition comprised the same enteral formulation (Nutrison, Nutricia Australasia, Sydney, NSW) throughout the audit period. Parenteral nutrition comprised:

- For the first 3 months of the audit, a glucose-based solution (70% dextrose 700 mL + Synthamin 17.8 L [Baxter Clinitec, Sydney, NSW]) infused continuously over 24 hours, with lipid (Intralipid 20% 500 mL [Pharmatel Fresenius Kabi, Sydney, NSW]) infused over 8 hours twice weekly (approximating 2245 kcal/day).
- For the second 3 months of the audit, a balanced PN solution (50% dextrose 1000 mL + Synthamin 17.5 L + Clinoleic 20% 500 mL [Baxter Clinitec, Sydney]) administered continuously over 24 hours (approximating 2280 kcal/day).

Data collection and statistical analysis

Data were collected retrospectively on all patients treated according to the intensive insulin protocol by interrogation of the master patient database in the ICU Clinical Information System (QS, GE Healthcare, Chalfont St Giles, UK). For analysis, the two 3-month audit periods are termed Glu (when the glucose-based PN regimen was used) and Lip (when the balanced, or lipid-based, PN solution was used). Comparisons were made between all patients in each period (GluALL versus LipALL), between patients who received PN at any time during their ICU stay (GluPN versus LipPN), and between patients who received only EN or intravenous dextrose (ie, EN, or PN never commenced) (GluEN versus LipEN).

We retrieved and analysed all blood glucose measurements for all patients throughout their ICU stay. We report the mean of all blood glucose measurements in each audit group, and also the percentage of all blood glucose recordings that fell within pre-defined ranges (hypoglycaemia = 0–2.2 mmol/L; low = 2.2–4.3 mmol/L;

target = 4.4–6.1 mmol/L; high = 6.2–11.9 mmol/L; and very high ≥ 12 mmol/L).

However, as the statistical analysis required individual data points to be independent, individual blood glucose measurements could not be used. We therefore calculated the median blood glucose value for each patient and, from these, determined group medians and interquartile ranges. Similarly, the percentage of blood glucose measurements falling in pre-defined ranges was determined for each

patient, and the median percentage for each range was calculated in each group.

For non-parametric data, differences between groups were analysed using the Kruskal–Wallis test with Dunn’s multiple comparison test post hoc. Differences between mean values were determined using ANOVA with Bonferroni’s multiple comparison test post hoc (GraphPad InStat, GraphPad Software Inc, San Diego, CA). Significance was accepted for *P* values less than 0.05. Caloric intake was normalised to days fed for comparison between groups before analysis.

Results

Patient demographic characteristics

Of the 322 patients admitted to the ICU during the audit period, 96 (30%) were treated according to the intensive insulin protocol. Their clinical characteristics on ICU admission are shown in Table 1. The most common admitting medical diagnosis was septic shock (27%), while the most common admitting surgical diagnosis was gastrointestinal neoplasm (20%). Two patients were postoperative cardiothoracic patients. Surgical patients were over-represented in the PN groups in comparison to the total patient cohorts and the EN groups. By nature of the inclusion criteria (expected to stay in ICU over 48 hours), the patients were seriously ill (mean APACHE II score, >25). Overall, about two thirds were male, but in the groups receiving PN this fell to about 50%. The LipPN group contained a greater proportion of patients with diabetes mellitus than did the other groups. Patients receiving PN had significantly longer stays in the ICU compared to those receiving EN or dextrose alone.

Blood glucose control

All blood glucose measurements obtained from the 96 patients treated according to the protocol were retrieved,

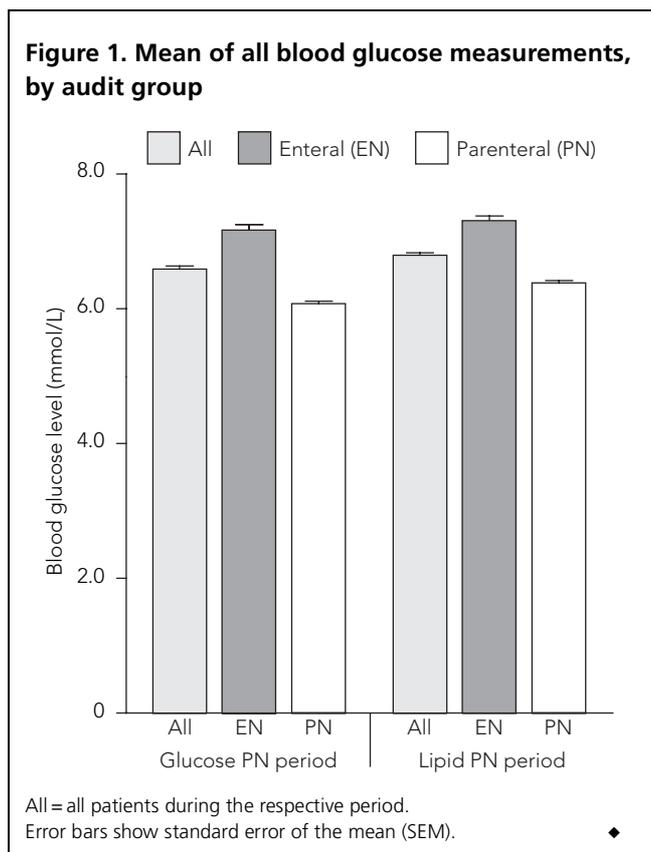
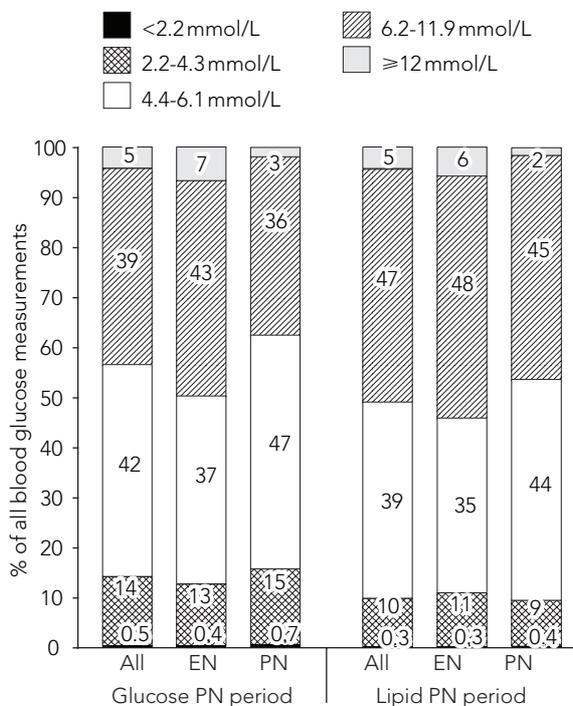


Table 2. Median blood glucose measurement for patients in each audit group and median percentage of blood glucose measurements for each patient falling in pre-defined ranges

Group	Median blood glucose (IQR) (mmol/L)	Median % of measurements falling in blood glucose range (IQR)				
		Target (4.4–6.1 mmol/L)	Hypoglycaemia (≤ 2.2 mmol/L)	Low (2.3–4.3 mmol/L)	High (6.2–11.9 mmol/L)	Very high (≥ 12 mmol)
GluALL	6.54 (5.98–7.4)	35.4 (21.3–47.4)	0 (0–0.35)	12.25 (6.9–16.9)	42.2 (33.8–54.2)	1.1 (0–8.1)
GluEN	6.75 (5.98–7.6)	33.1 (17.8–47.3)	0 (0–0)	12.3 (5.95–16.9)	42.8 (33.4–55.4)	0 (0–11.3)
GluPN	6.17 (5.9–7.3)	45.0 (40.6–48.2)	0.2 (0–1.15)	11.5 (8.5–18.0)	40.0 (34.3–52.1)	2.8 (0.5–7.7)
LipALL	6.95 (6.3–8.2)	28.5 (23.0–41.6)	0 (0–0.35)	8.5 (4.8–11.6)	47.4 (36.5–60.1)	12.2 (1.6–100)
LipEN	7.62 (6.6–9.12)	25.8 (17.9–37.7)	8 (3.6–12.5)	25.8 (17.9–37.7)	49.6 (36.5–60.1)	1.6 (0–12.2)
LipPN	6.38 (5.8–7.0)*	41.1 (29.7–56.0)	0 (0–1.6)	9.6 (5.9–11.3)	45.3 (34.9–60.5)	0 (0–2.9)

IQR = interquartile range. Glu = glucose-based parenteral feeding period. Lip = lipid-based parenteral feeding period. ALL = all patients during the respective period. EN = enteral nutrition. PN = parenteral nutrition. * *P* < 0.05 compared with LipEN.

Figure 2. Percentage of all blood glucose measurements falling in pre-defined ranges, by audit group



All = all patients during the respective period. EN = enteral nutrition. PN = parenteral nutrition. ♦

with 10 588 individual glucose results available for analysis, equating to one measurement approximately every 1.92 patient hours. The mean values of all blood glucose measurements in each of the audit groups are shown in Figure 1. Overall, mean blood glucose level was lower in patients in the PN groups compared with the EN groups. Table 2 shows the median blood glucose levels from individual patients. Median glucose level was significantly lower in the LipPN group than the LipEN group, but was otherwise similar between groups. Individual patients' blood glucose measurements were in the target range (4.4–6.1 mmol/L) on 25.8% to 45.0% of occasions depending on group. Patients in the PN groups had more blood glucose measurements within the target range than those in the EN groups, and the GluPN group had more measurements in the target range than the LipPN group.

Figure 2 shows the percentage of all blood glucose measurements falling within the pre-defined ranges. Hypoglycaemia was rare, but low blood glucose and hypoglycaemic events (ie, blood glucose ≤ 4.3 mmol/L) were more frequent in GluPN patients than in LipPN patients (Table 2). This difference was not statistically

significant. None of the hypoglycaemic events were associated with adverse clinical sequelae. There was no significant difference in the incidence of hyperglycaemia > 12 mmol/L between EN and PN patients in either feeding period, but fewer patients had extreme hyperglycaemia in the LipPN group compared with the LipEN or GluPN group.

Days fed, caloric intake and insulin requirements

The PN groups had more feeding days with significantly greater caloric intake per day fed than the EN groups. The PN groups required more insulin than their respective EN groups, but the LipPN group used less insulin than the GluPN group, although this difference did not reach statistical significance (Table 3).

Discussion

This observational audit found that, when using an intensive insulin therapy protocol, the use of PN compared with EN was associated with greater daily caloric intake. However, there were no significant differences in terms of glycaemic control or insulin requirements.

Recent evidence has demonstrated a mortality benefit from a strategy of intensive insulin therapy to achieve tight glycaemic control, and there are now at least five published trials in critically ill patients demonstrating benefits from this approach.^{2-5,15,16} In all cases, careful attention to nutrition has been emphasised, but there has been no systematic analysis of the impact of nutrition strategies on glucose control. Furthermore, it remains unclear as to whether it is the control of blood sugar *per se* or the administration of insulin that is the principal driver of the improved outcome from intensive insulin therapy.¹⁷ Van den Berghe's group has claimed that the control of blood sugar is the most important factor.¹⁸ If so, then nutritional management that promotes hyperglycaemia may result in both increased insulin requirements and poorer glycaemic control, limiting its potential benefit to patients.

When introducing the intensive insulin therapy protocol in our ICU, we were cognisant of the need to maintain

Table 3. Days fed, caloric intake and insulin usage

Group	Median days fed (IQR)	Mean kcal/day fed (SEM)	Median insulin usage (IU/day) (IQR)
GluEN	2 (0-5)	768 (327)	60.2 (46-121.5)
GluPN	10 (6.5-20)	1565 (305)*	108 (71.5-207.5)
LipEN	7 (0-26)	941 (332)	49.5 (27.8-88.2)
LipPN	12.5 (4-24)	1476 (461)*	88.9 (55.8-114.9)

Glu = glucose-based PN feeding period. Lip = lipid-based PN feeding period. IQR = interquartile range. * P < 0.05 compared with EN. ♦

caloric intake in patients receiving insulin and hence reviewed the nutrition management protocol. Based on Van den Berghe et al's initial protocol² and the guidelines developed by the ACCEPT (Algorithms for Critical-Care Enteral and Parenteral Therapy) study,¹ we introduced a 25% dextrose infusion from admission and emphasised the need to introduce EN or PN by the second day of admission at the latest. There is a possibility that this strategy increases the likelihood that patients will receive PN. This is firstly because hyperglycaemia induced by the dextrose infusion and poorly controlled in a critically ill patient on the first day of admission may adversely influence gastric emptying.¹⁹ Secondly, the strategy emphasises achieving caloric targets by the end of the second day, which may be difficult to achieve with EN alone.

Traditionally, PN is associated with hyperglycaemia,²⁰ and hence our hypothesis that use of PN while employing an intensive insulin therapy protocol would be associated with poorer achievement of desired blood glucose targets than use of EN. On the contrary, we observed that blood glucose measurements were more often in the target range and less often in the high ranges in patients receiving PN. We postulate that the better glycaemic control associated with PN reflects a superior pharmacokinetic profile of PN compared with EN, with easier administration and more reliable and consistent delivery of calories. This consistency facilitates glucose homeostasis and achievement of normoglycaemia with intensive insulin strategies.²¹ In critically ill patients, establishing EN is often difficult and slow, even with the implementation of dedicated EN feeding protocols and prokinetics.⁷⁻⁹ This often leads to underprovision of calories, which was well demonstrated in this audit. Added to this difficulty and delay are questionable levels of gastrointestinal absorption.

Debate continues as to the optimal route of nutrition in critically ill patients. Increasingly, the notion that EN is superior to PN in terms of mortality benefit has been brought into question.^{10,22,23} Nonetheless, the two most recent systematic reviews of PN versus EN have demonstrated an increase in infectious complications associated with PN.^{10,22} There is a clear relationship between hyperglycaemia and infection in critically ill patients.²⁴ However, the studies reviewed in these meta-analyses were conducted before publication of Van den Berghe's intensive insulin therapy study, raising the possibility that results might be different in the era of tight glycaemic control. Our observations suggest that this might be the case, as hyperglycaemia is not a feature of PN use in the setting of tight glycaemic control. Furthermore, a recent study also suggested that assiduously striving to achieve the nutritional intake targets in published guidelines may be associated with worse clinical outcomes, and that modest calorie restriction, which

would likely be associated with improved glycaemic control, may be preferable.²⁵

Our second hypothesis was that glycaemic control would be easier to achieve in patients receiving PN if the solution used was "balanced" (containing both dextrose and lipid as a source of calories) and infused continuously, rather than dextrose-based with small amounts of lipid given infrequently solely to prevent essential fatty acid deficiency. Better achievement of glycaemic control with LipPN in comparison with GluPN was shown in a previous study,²⁶ but we found no significant difference in the percentage of blood glucose measurements in the target range with LipPN compared with GluPN. LipPN patients displayed less hyperglycaemia and reduced insulin requirements, even though the group included more participants with diabetes mellitus.

It is possible that the longer ICU stays in the PN patients may have influenced the results. Blood glucose control tends to become easier as a patient's general condition stabilises, and insulin resistance settles.² Long-stay patients will therefore be more likely to have lower mean blood glucose values and a greater percentage of blood glucose measurements within the desired range. While none of the differences we observed reached statistical significance, we believe that our results suggest that concern about achieving glycaemic control should not influence the decision to use PN in critically ill patients. Furthermore, when PN is to be used, there is probably little difference between a glucose-based or balanced formulation containing lipid. However, there is the possibility that the insulin-sparing effect of the balanced solution when compared with the glucose-based solution may be of benefit, if it is accepted that glucose control rather than insulin dose is most important. Larger insulin doses have been correlated with increased mortality risk in critically ill patients.²⁷

Our audit had many limitations. It was a retrospective, single-centre, observational audit with a relatively small sample size, especially of patients who received PN. Furthermore, as it was conducted over the 6 months after the introduction of an intensive insulin therapy protocol, it is possible that the compliance of nursing staff with the protocol fell over time. The protocol is nursing-labour intensive and may be unpopular with staff. A reduction in compliance is suggested by the smaller number of patients treated according to the protocol in the second 3 months compared to the first. Reduced compliance might also explain the lack of a significant overall difference in blood glucose control between GluPN and LipPN patients, as there was poorer achievement of the target range in EN patients in the second 3-month period compared to the first. We provided feedback of the results of this audit to re-educate ICU nursing and medical staff about the protocol to optimise compliance. We believe that the findings indicate the need

for regular audit of target achievement when an intensive insulin protocol is in place, so that "protocol fatigue" can be recognised early, and remedial action taken.

Conclusion

We found that tight glycaemic control using an intensive insulin therapy protocol is better achieved with a feeding regimen that includes PN rather than EN alone. PN that contains lipid in a balanced formulation does not achieve better blood glucose control than does PN containing dextrose alone, although the former may be insulin-sparing and associated with less hyperglycaemia. Concern about worsening glycaemic control should not influence a decision to use PN in critically ill patients.

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