Addition of Insulin to Parenteral Nutrition for Control of Hyperglycemia

Adam McCulloch, MBChB1; Vishakha Bansiya, MBBS2; and Jeremy M. Woodward, PhD1

Abstract
Administration of parenteral nutrition (PN) may result in hyperglycemia in patients with preexisting diabetes or disease-related insulin resistance, and it can be associated with increased rates of complications. Treatment requires insulin therapy. Insulin can be administered subcutaneously, intravenously via a variable rate sliding scale, or by adding it directly to the PN. The last method is a potentially attractive technique for a number of reasons—it could deliver the insulin intravenously at a steady rate alongside carbohydrates, and in malnourished patients with little subcutaneous tissue, it may prevent the need for frequent insulin injections. Despite such potential advantages, the addition of insulin to PN remains controversial, largely with respect to the bioavailability of insulin in PN and resultant concerns of the risk of hypoglycemia. There is a paucity of long-term quality controlled studies to address this question. The available literature suggests that, at least in the short term, insulin addition to PN can achieve reasonable glycemic control with low rates of hypoglycemia, and the technique compares favorably with the use of long-acting insulin preparations. This literature review finds a wide range of values reported for insulin availability via PN, ranging from 44% to 95% depending on the type of PN container material used and the presence of added vitamins and trace elements. Few studies looking at glycemic control among patients receiving home PN were found, and larger prospective trials are needed to assess the efficacy and safety of this technique in this patient group. (JPEN J Parenter Enteral Nutr. 2018;42:846–854)

Keywords
diabetes mellitus; glycemic control; hyperglycemia; intestinal failure; intravenous insulin; research and diseases

Hyperglycemia is reported in >50% of patients receiving parenteral nutrition (PN).1 In preexisting diabetes mellitus, intravenous carbohydrate delivery may result in impaired regulation of blood glucose (BG) levels. However, impaired glucose tolerance or overt diabetes may be unmasked or exacerbated by underlying illness, such as pancreatic disease, sepsis, burns, trauma, or medication side effects. These conditions are characterized by enhanced gluconeogenesis, glycogenolysis, insulin resistance, and impaired glucose oxidation mediated by increased levels of counterregulatory hormones and cytokines; all of which, in combination with the extra PN glucose load, contribute to hyperglycemia.2 In modern practice, parenteral calorie prescriptions have reduced as a result of improved understanding of the energy requirements associated with disease states. However, intravenous delivery makes excess carbohydrate delivery easy to achieve, and the glucose oxidation and storage capacity vary greatly in sick patients depending on the cytokine and hormonal milieu. Glucose homeostasis with PN may be further impaired by the lack of incretins (eg, glucose-dependent insulino tropic polypeptide and glucagon-like peptide 1) released by intestinal K and L cells following enteral intake. Studies have shown improved glucose control with enteral feeding over PN, supporting this notion.3,4

PN-induced hyperglycemia is not a trivial complication. It results in higher rates of admission to the intensive care unit, longer hospital stays, and higher mortality rates when compared with patients without hyperglycemia.5,6 One study showed that each 9-mg/dL increase in BG >113 mg/dL resulted in a 7%–10% increase in the risk of infection and organ dysfunction.7 Another large prospective study of noncritically ill patients receiving PN showed that patients with a mean BG of 180 mg/dL had a 5.6-times-greater risk of mortality than those with a mean BG <139 mg/dL.8 While hyperglycemia itself may reflect underlying disease

From the 1Cambridge Intestinal Failure and Transplant, Addenbrooke's Hospital, Cambridge, United Kingdom; and the 2Institute of Metabolic Medicine, Addenbrooke's Hospital, Cambridge, United Kingdom.
Financial disclosure: None declared.
Conflicts of interest: None declared.
Received for publication May 15, 2017; accepted for publication July 5, 2017.
This article originally appeared online on August 9, 2017.
Corresponding Author:
Jeremy M. Woodward, PhD, Cambridge Intestinal Failure and Transplant, Addenbrooke's Hospital, Box 133, Hills Road, Cambridge, CB2 0QQ, UK.
Email: jeremy.woodward@addenbrookes.nhs.uk
severity, when exacerbated in the context of PN, it is associated with increased rates of morbidity and mortality.7,9,10

There is compelling evidence for poorer outcomes in association with hyperglycemia; however, evidence of benefits of intensive management to tight glycemic ranges outside of selected critical care units is less clear, with significant concerns from recent studies of increased risk of hypoglycemia.11 While more robust evidence is awaited, the consensus supports treatment of hyperglycemia but to moderate glycemic goals. The American Diabetes Association and American Association of Clinical Endocrinologists recommend BG measures of 140–180 mg/dL.12

Various single and combination approaches to management of PN-related hyperglycemia have been reported, including intravenous insulin infusions,2,9,13 subcutaneous insulin administration, and direct addition of short-acting insulin to PN.14-16 Of these, direct addition of short-acting insulin to the PN mixture offers certain advantages. Expert opinion suggests that by consolidating the insulin dosage within the PN formula, a steady supply of insulin with the formula provides a smoother glycemic profile without increased risk of hypoglycemia by reducing discordance between insulin dosing and PN administration.17 However, there remain concerns about the availability and delivery of insulin and, thereby, the efficacy as well as risks of hypoglycemia for this mode of insulin delivery. Given the potential for adverse events, the American Society for Parenteral and Enteral Nutrition recommends that “insulin use in PN should be done in a consistent manner adhering to a defined protocol, in which healthcare personnel have adequate knowledge.”18

This review describes existing knowledge on the quantification of insulin release from PN and summarizes current clinical experience with the use of insulin in PN among hospital inpatients in terms of efficacy of glycemic control and risk of hypoglycemia. We describe the potential for the use of this technique among patients receiving PN in their homes, rather than in the hospital, and we make practical recommendations for the use of insulin in PN and further research in this area.

Methods
We identified relevant papers by searching the medical databases Medline (1996–February 2017) and Embase (1974–February 2017). The search of the electronic databases used the following terms: (Insulin.mp. or Insulin/) and (parenteral nutrition.mp. or parenteral nutrition/) and (hyperglycemia.mp. or hyperglycemia/). A total of 560 studies were generated with these search terms, with relevant articles selected following screening of the titles, keywords, and abstracts. Studies that evaluated any aspect of the addition of insulin into PN were chosen, whether interventional or observational. Excluded articles included those with no relevance to the topic, general review articles on hyperglycemia management in PN, studies involving neonates, and conference abstracts.

In addition to the Medline/Embase search, hand searching with the online search engine Google was conducted to identify other published and unpublished data on the topic.

Results
Selected Articles
Fifteen papers were selected, mainly including observational studies and retrospective reviews of practice. Laboratory studies were selected for inclusion in this review, as they reveal important information regarding the availability of insulin after addition to the PN and the effect of certain PN constituents on the added insulin. Table 1 summarizes the chosen studies, including the study design, participants, and findings.

Insulin Availability in PN
A potential barrier to the more widespread use of insulin in PN has been the uncertainty over the quality of the admixture of insulin with the PN and the availability and consistency of insulin delivery in the feed. Studies on this topic have demonstrated decreased insulin availability from a variety of intravenous fluids due to adsorptive losses to delivery systems. This literature review revealed reported insulin availability from PN to range from 44% to 95%.19-22 This wide difference is most likely accounted for by the differing PN compositions, PN container material, assay methods, and type of insulin used in the analyses.23 Yu et al,22 for example, found insulin adsorption on the ethylene vinyl acetate–containing bag to be 62.7%, compared with 6.3% on the glass material.

Another finding to emerge from some of the studies is the differences in insulin availability with the addition or removal of certain constituents in the PN. Marcuard et al20 showed that insulin availability was significantly reduced if it contained the amino acid preparation HepatAmine as compared with FreAmine (88% vs 94%). Weber et al19 found that the addition of electrolytes and vitamins improved insulin availability. Indeed, the presence of vitamins and trace elements in the PN appears to have a dramatic effect on the availability of insulin added to the bag—their removal reduced the available insulin in PN from 96% to 4.5%.21 Furthermore, the availability of insulin in PN decreases during the infusion: this same study demonstrated that in complete PN, the recovery of insulin was initially 96% 1 hour into the infusion but only 87.3% 1 hour prior to its completion. This would suggest that there is a relatively slow process of adsorption of insulin to container surfaces or interaction with other PN constituents or that products of degradation of constituents that may accumulate during
<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>Participants</th>
<th>Study Focus</th>
<th>Insulin-in-PN Protocol</th>
<th>Significant Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hakeam (2016)</td>
<td>RCT</td>
<td>61 surgical inpatients. Patients with type 1 diabetes excluded.</td>
<td>Comparison of glargine vs insulin in PN for glycemic control.</td>
<td>Amount of insulin added to PN equal to 80% of final-day insulin total daily dose via subcutaneous sliding scale from day 0 to 4. Comparison arm had same dose as single subcutaneous glargine dose. If BG high, then dose increased by 40%–60% of total dose on the previous day. Decreased by 50% of dose if BG low.</td>
<td>No significant differences between the 2 groups.</td>
</tr>
<tr>
<td>Oghazian (2015)</td>
<td>RCT</td>
<td>21 surgical inpatients with no history of sepsis, diabetes, significant renal impairment.</td>
<td>Glargine vs insulin in PN for glycemic control.</td>
<td>Initial amount of insulin added to PN determined by BG levels on the previous day (eg, if BG = 8.3–11 mmol/L, then 15 U of insulin per 100 g of PN glucose added to PN). The amount of insulin increased or decreased depending on subsequent readings.</td>
<td>No statistically significant differences in the percentage of BG levels in the goal, hyperglycemic, and hypoglycemic ranges were found between the groups receiving insulin in PN or glargine.</td>
</tr>
<tr>
<td>Shizgal (1989)</td>
<td>RCT</td>
<td>135 patients without diabetes mellitus.</td>
<td>Evaluation of body composition changes with insulin added to PN, compared with PN alone.</td>
<td>30 U of insulin added to each liter of PN.</td>
<td>Correction of malnourished state improved to greatest extent in group receiving insulin in PN.</td>
</tr>
<tr>
<td>Jakoby (2011)</td>
<td>Prospective cohort</td>
<td>22 inpatients, with diabetes and without.</td>
<td>Review of insulin addition to PN vs ad hoc treatment.</td>
<td>Overall insulin requirements calculated (eg, 1 U of insulin per 20 g of PN glucose, 1 U per 10 g of PN glucose in well-controlled diabetes). Two-thirds added to PN with remaining third injected subcutaneously in 3-4 divided doses. Additional basal insulin may be needed depending on whether patient had a history of diabetes or not.</td>
<td>Mean BG = 7.7 mmol/L in protocol group and 8.8 mmol/L for the control group. Proportion of BG values in the target range = 60% in the protocol group and 35% in the control group (P = .0001). Hypoglycemia: 3% in protocol group vs 1% in control group (P = .012). No severe hypoglycemia detected.</td>
</tr>
<tr>
<td>Olveira (2015)</td>
<td>Prospective cohort</td>
<td>605 inpatients, noncritically ill. 35.8% were receiving insulin in PN.</td>
<td>Prospective multicenter review of patients receiving PN to determine hypoglycemia prevalence and risk.</td>
<td>Not discussed.</td>
<td>Increased risk of hypoglycemia with intravenous insulin (as a separate infusion or added to PN), odds ratio = 1.6 (95% CI, 0.7–4.2; P = .3).</td>
</tr>
<tr>
<td>Sajbel (1986)</td>
<td>Case series</td>
<td>16 inpatients who developed hyperglycemia with PN. 5 of the 6 had a history of diabetes.</td>
<td>Evaluation of separate insulin infusion to control hyperglycemia. Cost comparison with insulin addition to PN.</td>
<td>All patients received separate intravenous insulin infusions.</td>
<td>Separate insulin infusion more cost-effective than adding insulin to PN.</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>Participants</th>
<th>Study Focus</th>
<th>Insulin-in-PN Protocol</th>
<th>Significant Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinnare (2013)</td>
<td>Retrospective cohort study</td>
<td>1657 inpatients receiving PN, with diabetes and without.</td>
<td>Determining the characteristics increasing the risk of hypoglycemia in patients receiving PN and insulin.</td>
<td>N/A</td>
<td>Insulin addition to PN not associated with increased risk of hypoglycemia. Strongest predictors: receiving PN in the intensive care unit, history of diabetes, days receiving PN, and an insulin drip.</td>
</tr>
<tr>
<td>Pleva (2009)</td>
<td>Retrospective review</td>
<td>50 patients receiving PN (not in intensive care), with diabetes and without. An unspecified number of patients received insulin in PN.</td>
<td>Evaluated the frequency of hyperglycemic and hypoglycemic events.</td>
<td>Not discussed.</td>
<td>1.4 hyperglycemic events per patient. Low rates of hypoglycemia in patients receiving insulin in PN (2 of 15 episodes).</td>
</tr>
<tr>
<td>Varayil (2015)</td>
<td>Retrospective review</td>
<td>93 outpatients, 39 of whom received insulin in PN. Nondiabetic.</td>
<td>Review of the Mayo Clinic's patients receiving home PN, including prevalence of hyperglycemia and complications.</td>
<td>Not discussed.</td>
<td>42% required insulin in PN. Infection and complication rates similar between the insulin and noninsulin cohorts.</td>
</tr>
<tr>
<td>Hongsermeier (1993)</td>
<td>Case series</td>
<td>20 inpatients with type 1 or 2 diabetes prior to index admission.</td>
<td>Evaluation of protocol for insulin addition to PN.</td>
<td>Two-thirds of the previous day's total subcutaneous correction doses added to PN. Insulin then adjusted to achieve stable BG readings and an overall PN glucose:insulin ratio established.</td>
<td>Good average BG control achieved (11.3 mmol/L in infected group, 10.7 mmol/L in noninfected group).</td>
</tr>
<tr>
<td>Valero (1996)</td>
<td>Case series</td>
<td>91 inpatients, including those with a history of diabetes.</td>
<td>Management of hyperglycemic patients receiving PN.</td>
<td>Initially, 150–200 g of glucose in PN given. Two-thirds of previous day's insulin added to PN. When values controlled at 11.1 mmol/L, glucose increased in PN and insulin adjusted incrementally.</td>
<td>74 patients (81%) had BG &lt; 11.1 mmol/L and 89% had BG &lt; 13.9 mmol/L.</td>
</tr>
<tr>
<td>Christianson (2006)</td>
<td>Laboratory study</td>
<td>N/A</td>
<td>Evaluation of insulin availability in standard PN preparation.</td>
<td>N/A</td>
<td>Recovery of insulin from PN, 95%; when multivitamins and trace elements removed, insulin recovery only 5%.</td>
</tr>
<tr>
<td>Marcuard (1990)</td>
<td>Laboratory study</td>
<td>N/A</td>
<td>Evaluation of insulin availability in standard PN preparation.</td>
<td>N/A</td>
<td>Insulin availability, 90%–95%.</td>
</tr>
<tr>
<td>Weber (1977)</td>
<td>Laboratory study</td>
<td>N/A</td>
<td>Evaluation of insulin availability in standard PN preparation.</td>
<td>N/A</td>
<td>Insulin availability 53%–56%.</td>
</tr>
<tr>
<td>Yu (2016)</td>
<td>Laboratory study</td>
<td>N/A</td>
<td>Evaluation of insulin availability in standard PN preparation.</td>
<td>N/A</td>
<td>Insulin availability: 47.3% when ethylene vinyl acetate bag used, 93.7% when glass used.</td>
</tr>
</tbody>
</table>

BG, blood glucose; N/A, not applicable; PN, parenteral nutrition; RCT, randomized controlled trial.
the hanging time (e.g., lipid peroxides) might interact with insulin or its binding to other components. The reasons for the effect of the PN container material and added vitamins and trace elements on insulin availability are not fully understood. Various hypotheses have been put forward, including the possibility that components of the multivitamins may form complexes with insulin, which prevents adsorption to glass and plastic. Alternatively, anions may form from the multivitamins that occupy sites to which insulin would otherwise bind. Clearly, the chemistry of PN is highly complex, and the variety of ways and the physicochemical parameters with which insulin interacts with the constituents, as well as the material of the bag, require further investigation.

In practical terms, the variable availability of insulin added to PN would serve to limit its use to standardized bags where the insulin delivery is already established or to patients with stable PN prescriptions. In the latter case, any changes to the formulation might have an impact on the insulin effect and necessitate closer BG monitoring or a temporary change of insulin delivery technique.

Clinical Studies of Efficacy of Insulin Delivered in PN

Interestingly, the first clinical study of insulin admixed with PN was not to counteract coincidental hyperglycemia but to use insulin as an anabolic agent to promote a faster correction of the malnourished state. Nevertheless, it demonstrated the potential applicability of this technique in more routine clinical settings.

Hongsermeier and Bistrian were the first to evaluate a protocol for insulin addition to PN by retrospective review of 16 patients and a prospective study of 4 eligible patients managed by an algorithm that they had developed and that was in effect at their institution for the 8 years prior to the review. All patients had type 1 or 2 diabetes and required insulin preadmission. Initial average glucose content of the PN was 100 g for patients with type 1 diabetes and 150–200 g for those with type 2 diabetes. The insulin protocol consisted of adding two-thirds the amount of total correctional doses of subcutaneous short-acting insulin required over the previous 24 hours to the PN the following day. The insulin content was then altered to achieve stable BG readings (at least 1 reading <250 mg/dL), and an overall PN glucose:insulin ratio was calculated. The PN glucose concentration was then advanced and BG control achieved by maintaining the established PN glucose:insulin ratio. Glycemic data were measured over a period of 3 consecutive days, starting when the PN prescription had stabilized.

The researchers analyzed results from patients with and without ongoing infection. BG levels were adequate, with values of 203 and 194 mg/dL in the infected and noninfected groups, respectively, over a 3-day study period. Significant hypoglycemia (<59 mg/dL) was not seen. The researchers thus concluded that their technique of BG control “demonstrated safety, efficacy and clinical applicability.”

Indirect evidence for the effectiveness and safety of insulin addition to PN comes from other studies and case series where this aspect was not the primary objective, although they did describe the use of insulin addition to PN as an established method to achieve glycemic control. Valero and colleagues published a retrospective case series from Madrid evaluating their experience managing hyperglycemia in patients receiving PN via an individualized protocol-driven prescription. The group retrospectively identified 91 inpatients managed in their institution over a 1-year period who received insulin added to their PN as part of routine clinical practice for managing PN-induced hyperglycemia. The insulin dose determined by the protocol was equivalent to two-thirds of the previous day’s administered insulin added to the PN bag with subsequent changes to the insulin content based on BG readings. Patients with and without a history of diabetes were included. PN was provided for 14 days. As with the Hongsermeier and Bistrian study, the results revealed acceptable glycemic control—with average BG readings of 169 and 176 mg/dL in patients without and with sepsis, respectively. None of the included patients developed hypoglycemia, ketoacidosis, or nonketotic hyperosmolar coma during PN.

Along similar lines, Jakoby and Nannapaneni prospectively evaluated an insulin protocol for 25 episodes of PN-induced hyperglycemia in 22 patients, comparing it with historical controls who had insulin variously delivered by supplemental subcutaneous sliding scale, scheduled basal insulin, or insulin added to the PN. The protocol calculated overall insulin requirements based on presence or absence of diabetes, steroid treatment; and current glycemia (1 unit per 5 g of PN glucose in a patient with known diabetes/steroid treatment and BG >200 mg/dL, 1 unit per 10 g of PN glucose in a patient with known diabetes/steroid treatment and BG <200 mg/dL; 1 unit per 20 g of PN glucose in a patient with hyperglycemia associated with PN but no preexisting diabetes). Two-thirds of the calculated dose of insulin was then added to the PN. The remaining one-third would be administered subcutaneously as neutral protamine Hagedorn insulin in 3 to 4 divided doses. Patients with a history of diabetes received additional neutral protamine Hagedorn insulin (0.15 or 0.25 U/kg/d in patients with BG <200 or >200 mg/dL, respectively) in 3–4 divided doses. The researchers found that the mean BG after the first day of PN was 139 mg/dL for the protocol group and 158 mg/dL for the control group. Proportion of BG values in the target range of 79–140 mg/dL was 60% in the protocol group and 35% in the control group (P < .0001). The patients receiving insulin by protocol achieved 93% of their requirements in a scheduled manner, whereas in the control group, 66% of insulin requirements were given as...
supplemental correctional doses. The researchers concluded that the efficacy of glycemic control by insulin given in the PN per the protocol was significantly superior to that not driven by protocol. Note, however, that this was not a study comparing insulin in the PN with that given by separate infusion alongside—some of the patients within the control group also received their insulin in the PN (numbers not given), and the protocol required more intensive checking of BG levels (4 hourly rather than 6 hourly).

Two studies compared the use of insulin in PN with subcutaneous basal insulin (glargine). Interestingly, both these studies used insulin in PN as the comparator and sought to validate the use of basal insulin in this group of patients, implying that in their practice, addition of insulin to PN was the more established therapeutic method.

The study by Oghazian et al was a prospective randomized open-label trial that compared glycemic outcomes for patients in intensive care units receiving PN. Insulin addition to PN was based on glucose values on the first day of PN administration. Doses were subsequently adjusted every 24 hours based on preceding-day readings and use of additional subcutaneous correction doses. After 3–5 days, patients were randomized to continue to receive insulin via PN or to change to subcutaneous basal insulin (glargine) at 80% of the dose for a further 3 days (21 patients in each arm). No significant difference in glycemic control was demonstrated, with approximately half the glucose readings in each group within the target glucose of 110–180 mg/dL.

No patients in the insulin-in-PN group developed hypoglycemia (<70 mg/dL), while 4 patients in the basal insulin group did. Of note, the protocol specifically excluded patients with diabetes or on steroids and called for addition of escalating doses of insulin to PN at glucose ranges generally regarded within range (commencing at 100 mg/dL). This limits the generalizability of the findings but nonetheless demonstrated comparable efficacy and safety in this group.

The study by Hakeam et al also compared the use of insulin in PN with basal insulin glargine in the control of hyperglycemia for patients receiving PN outside of intensive care in a prospective randomized open-label trial. They recruited a total of 67 PN episodes in 61 patients. All patients received subcutaneous insulin by a correction sliding scale based on glucose readings. On day 4, patients were randomized to receive 80% of the previous day’s total insulin as either basal insulin glargine or insulin added to PN for a further 4 days. Dose adjustments were made daily depending on glucose readings. No difference was found in overall glycemic control, with roughly half of glucose readings in each group in the target range of 140–180 mg/dL. Hypoglycemia rates were low, with 2 patients in each group developing 6 episodes (4 for insulin in PN vs 2 for glargine) and none reported in either group <50 mg/dL. This study was more heterogeneous but still excluded patients with type 1 diabetes or on steroid therapy, affecting once again the generalizability but demonstrating no significant negative impact of using insulin in PN.

**Risks of Hypoglycemia Associated With Insulin in PN**

As well as efficacy, a key concern about adding insulin directly to PN is the danger of inducing hypoglycemia. Reassuringly, the aforementioned studies all demonstrated low rates of hypoglycemia. The 2 case series reported no significant episodes of hypoglycemia, but the retrospective nature of these studies may have led to underreporting. The improved glycemic control versus a historical control group was associated with a higher incidence of all hypoglycemia (defined as BG <80 mg/dL), 3% vs 1% (P = .012), but numbers remained low overall and, importantly, no episodes of severe hypoglycemia were seen (BG <40 mg/dL). A further report showed a low incidence of hypoglycemia associated with insulin in PN, although the number of patients treated via this route was unspecified.

Two other studies specifically evaluated the factors associated with hypoglycemia during PN. Kinnare et al retrospectively reviewed 1657 cases of patients who received PN and insulin (subcutaneous, variable rate intravenous insulin infusion [VRIII], or added to PN) to determine the factors predisposing to hypoglycemia during PN. They found that patients commencing PN in the intensive treatment unit receiving insulin via VRIII, and with a history of diabetes, days receiving PN, intensive treatment unit admission, and method of insulin dose calculation. The study by Olveira and colleagues prospectively analyzed the occurrence of hypoglycemia in 605 patients receiving PN across 19 Spanish hospitals. Of these 605 patients, 433 (71.6%) received insulin at some time during their PN infusion, with 35.8% of these receiving insulin added into PN. Overall incidence of hypoglycemia (BG <70 mg/dL) was low, at 0.82 per 100 days receiving PN. However, as the subgroup of patients receiving insulin via PN were not evaluated separately from patients receiving insulin through a separate intravenous infusion, conclusions cannot be made about the specific hypoglycemia risk attributable to addition of insulin to PN. Using regression analysis, the authors showed an increased risk of symptomatic hypoglycemia with intravenous insulin (as a separate infusion or added to PN), with an odds ratio of 5.1 (95% CI, 1.1–25.5; P = .05). Other significant risk factors for hypoglycemia in this group included patients with lower body mass index, greater glucose variability, and increased duration of PN.

The available data, although sparse, suggest that insulin can be delivered safely to inpatients who are being carefully monitored.
Insulin Added to Home PN

A recent review of the Mayo Clinic’s home PN (HPN) cohort found that 39 of 93 patients (42%) without pre-existing diabetes developed hyperglycemia while receiving home PN and were managed with insulin mixed with the PN therapy.30 Within the limits of a short follow-up period (3 years), the risk of death, new-onset nephropathy, retinopathy, heart failure, or peripheral neuropathy was no different between those with and without hyperglycemia who were receiving insulin in the PN, and overall rates of complications were very low in the entire cohort. The efficacy of therapy—for instance, HbA1c levels—was not recorded. All patients with preexisting diabetes and patients receiving corticosteroids were excluded. There are no other reports in the literature of the use of insulin added to PN in the home environment or for longer periods.

Discussion

The addition of insulin to PN is a physiologically attractive and potentially simple technique to treat hyperglycemia. As a result, its use is generally widespread,31 although paradoxically discouraged due to concerns over efficacy and safety. There is very little available literature on which to base any recommendations about its use. Analyses of insulin release from PN demonstrate wide variability and thereby suggest that caution is appropriate. The nature of the chemical interactions requires further elucidation if consistency and predictability are to be achieved. In hospital settings, the frequency of BG monitoring and close supervision improve the safety of insulin infusions; however, the instability of patients may require frequent alterations in PN composition with unknown effects on insulin delivery. Current guidelines note the discrepancy between current practice and the evidence base17 and fail to make recommendations.

This review highlights the paucity of clinical studies evaluating the practice of adding insulin to PN in patients receiving PN at home. The causes and management of dys-glycemia in HPN patients differ significantly from hospital inpatients. The former are more likely to have primarily impaired glucose handling, rather than stress hyperglycemia due to acute illness. HPN patients are more likely to be on stable insulin and PN prescriptions and therefore less likely to experience wide day-to-day fluctuations in BG measures as compared with inpatients. However, differences in the way in which PN is delivered in the home setting versus a hospital may make glycemic control more challenging. Feed may be infused overnight for 12–14 hours, and patients may receive no carbohydrates outside the infusion period, unlike the potential for continuous infusion in the hospital. The overnight period when the patient is least alert is therefore the time when glycemic control becomes challenging to monitor and poses potential risks of poor control or severe hypoglycemia. Moreover, existing insulin preparations may not adequately match the glycemic profile induced by intermittent PN regimens, resulting in hyperglycemia on commencement of feed and/or rebound hypoglycemia after it stops.

Given these differences, it is difficult to translate the results of the available clinical studies, performed mainly among hospital inpatients, into practical recommendations in the HPN community. This latter group, however, represents the patients most likely to benefit from optimal insulin delivery in association with PN to maximize insulin-mediated glucose utilization. Potential advantages to this mode of insulin delivery include reduced risk of unopposed insulin delivery due to simultaneous administration of insulin and PN, stable PN prescription for long periods, and increased opportunity to titrate to a stable insulin dose and achieve glycemic stability. In addition, the potential stability of BG levels may over time enable less frequent BG monitoring and limit the resulting negative lifestyle impact.

Future studies should therefore focus on comparing glycemic control with different modes of insulin delivery in the HPN cohort. In this group, the use of a separate intravenous infusion of insulin through a second lumen alongside the PN is not practical, given the need for frequent monitoring and dose adjustment. Subcutaneous basal insulin, with or without bolus doses, may not adequately match the glycemic profile, depending on the PN regimen used, and so carries a risk of hypoglycemia, should PN be unexpectedly interrupted after insulin has been administered. Though not routinely available for this indication in the United Kingdom, the use of continuous subcutaneous insulin infusion is a potential option and may lower the aforementioned risk, as insulin is infused continuously. However, it still depends on early detection of PN interruption to stop or reduce insulin delivery. This could be further enhanced by coupling with a continuous glucose monitoring sensor that could alert to falling glucose levels and potentially suspend insulin delivery. As the technology currently stands, a significant amount of patient education and engagement is essential to make this safe and practical to use. This makes the codeelivery of PN and insulin in the same infusion an attractive option.

In terms of current practical recommendations, clinicians should be aware of the highly variable and unpredictable insulin requirements that accompany acute severe illness (e.g., infection and inflammation). Therefore, initially insulin should not be added to PN unless (1) a stable blood sugar has been achieved by other means alongside the PN and (2) the PN prescription is consistent. Most insulin protocols of the included studies used an initial “runoff” period of VRIII or subcutaneous insulin to determine insulin requirements prior to adding insulin to PN. The variability of insulin release from PN and the fact that
standard ratios of insulin to carbohydrate may not translate into predictable insulin delivery underscores the importance of initially achieving stable BG readings. A target BG range of 140–180 mg/dL for hospitalized patients is suggested. Only regular short-acting insulin should be added to the PN. The amount of insulin added to the PN depends on the duration of the infusion and its overlap with subcutaneous insulin to meet interfed basal requirements, and whether the patient has preexisting diabetes or concomitant therapy that affects glycemia, such as steroids and glycemic targets. In the hospital, a VRIII may be the best way to determine initial requirements, and it requires the presence of local expertise to oversee safe transition to insulin in PN. BG measurements in the hospital should be monitored 4 hourly, during and after the infusion, but may need to be more frequent if unstable. Transition to adding insulin to the PN should be done at a time of relative stability in the course of the acute illness. Significant changes to the composition of the feed or clinical circumstances in hospital patients may require a return to insulin alongside the PN, rather than its addition to PN, until stability is regained. Above all, a close multidisciplinary team setup involving nutrition and diabetes teams is important. Patients discharged home while receiving PN can continue their insulin-in-PN regimen if glycemic stability has been established in the hospital. Education and engagement of the patients and/or their carers is essential to ensure safe transition and monitoring. Close monitoring and follow-up are required on discharge in view of changes in activity and insulin requirements at home versus the hospital. Attention needs to be paid to the possibility of early hyperglycemia after feed initiation and postfeed rebound hypoglycemia, and PN pump settings may need to be adjusted to allow for a “ramp-down” period of infusion rather than abrupt cessation. Again, communication between the nutrition and diabetes team with respect to changes to PN composition will be essential to enable timely review of insulin requirements.

In conclusion, the few available studies support the use of insulin in PN for hospitalized patients on stable regimens, demonstrating good glycemic control and safety profile. There is no information available on the safety or efficacy of insulin in PN for patients at home, with only 1 report suggesting that this approach may be safe for patients without preexisting diabetes who experience feed-related hyperglycemia. However, given that this practice is relatively common and may significantly benefit such patients, there is a need for the efficacy and safety of this technique to be fully established via larger studies using standard protocols that will allow clear guidance to be formulated.

**Statement of Authorship**

A. McCulloch and J. M. Woodward equally contributed to the conception and design of the research. All authors contributed to the acquisition, analysis, and interpretation of the data; drafted the manuscript; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

**Supplementary Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**References**


