Intermittent gastric feeds lower insulin requirements without worsening dysglycemia: A pilot randomized crossover trial

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ABSTRACT

Introduction: We hypothesized that critically ill medical patients would require less insulin when fed intermittently.

Methods: First, 26 patients were randomized to receive intermittent or continuous gastric feeds. Once at goal nutrition, data were collected for the first 4-hr data collection period. Next, the enteral feed type was switched, goal nutrition was repeated, and a second 4-hr data collection period was completed. The primary endpoint was the total amount of insulin infused; secondary endpoints were glucose concentration mean, maximum, minimum, and standard deviation, as well as episodes of hypoglycemia.

Results: Sixteen of the 26 patients successfully completed the protocol. One patient experienced a large, rapid, and sustained decline in insulin requirement from liver failure, creating a bias of lesser insulin in the intermittent arm; this patient was removed from the analysis. For the remaining 15 patients, the average total amount of insulin infused was 1.4 U/patient/h less following intermittent feeds: \( P = 0.027, \) 95% confidence interval (0.02, 11.17), and effect size 0.6. Secondary endpoints were statistically similar.

Conclusions: Critically ill medical patients who require an insulin infusion have a reduced insulin requirement when fed intermittently, whereas dysglycemia metrics are not adversely affected. A larger clinical study is required to confirm these findings.

Key Words: Continuous tube feedings, enteral nutrition, intermittent tube feedings, total insulin infused

INTRODUCTION

Healthy controls secrete more insulin when fed intermittently, rather than continuously.\(^1\) Furthermore, a numerical model of stress hyperglycemia demonstrated similar results for patients maintained on an insulin infusion.\(^2\) It was, therefore, hypothesized that critically ill medical patients would have a reduced insulin infusion requirement when fed with intermittent gastric feeds (IGF) rather than continuous gastric feeds (CGF). If correct, IGF might be an inexpensive adjunct to stress hyperglycemia treatment, perhaps reducing patient complications\(^3\) such as intestinal,\(^4\) hepatic,\(^5\) and gallbladder dysfunctions;\(^6\) a decreased splanchnic blood
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flow;[1] and a reduced ability to maintain muscle mass;[7] thereby reducing health-care costs.

**METHODS**

**Design**
This was a prospective, nonblinded randomized controlled crossover trial performed in a 20-bed government medical intensive care unit (MICU) between September 2016 and October 2017. An Institutional Review Board approved the trial protocol.

**Patients**
Inclusion criteria are patients aged between 18 and 90 years, anticipated MICU admission duration >72-h, and an indication for enteral nutrition without planned feed interruptions for at least 48-hr. Exclusion criteria barred trial entry to patients with a contraindication to gastric feeds, any previous gastric resection, and hemodynamic instability determined by high vasopressor requirements: norepinephrine, epinephrine, dopamine, and dobutamine >5 (µg/min); Vasopressin >0.04 (U/min) and Milrinone >0.375 (µg/kg/min). An anatomic reason for impaired intestinal nutrient absorption (previous surgery leaving <200 cm of small bowel length) or a contraindication to the enteral feed formula Osmolite® (to include potassium >6.4 (mEq/L) absent a plan for dialysis) were also exclusions. In addition, an ideal body weight >85 kg and a positive pregnancy test for females <60 years of age were used.

**Procedures and randomization**
Patients who completed the trial participated in two 4-h data collection periods: 5 data points separated by 1-h intervals when insulin infusion rate and glucose concentrations were recorded. Blood draw sources, in order of preference, were arterial lines (RAPIDpoint® blood gas instrument) and central lines (Nova Stat Strip Express Glucometer). Hourly data was collected only if insulin infusion was initiated. Short data collection periods were completed within 12-hr so the severity of patients’ stress hyperglycemia would not change significantly during the protocol. Computer random number generator determined randomization to either IGF or CGF first (performed by RJS); results were stored in sealed envelopes. A single author (TJS) enrolled all patients, and the trial protocol is outlined in Figure 1.

**Calculation of CGF goal rate and IGF goal volume**
Twenty-four caloric (25 kcal/kg/day) and protein (1.5 g/kg) requirements were calculated for Osmolite® 1.2; Actual body weight was used for body mass index (BMI) <30, and ideal body weight was utilized for BMI >30.[8] The advancement of feeds to goal, and management of feed intolerance (FI), was governed by protocol.

**Steady-state intervals**
Before entering any data collection periods, patients were fed at goal volume or rate for 4-hr to establish a glucose-insulin “equilibrium,” [Figure 1].

**Insulin infusion protocol**
If two consecutive blood glucose checks separated by 1 h were >159 (mg/dl), then a regular insulin infusion was used to maintain the blood glucose values in the range of 140–180 (mg/dl), and the infusion rate was adjusted based on hourly glucose concentration values.

**Measures**
The primary endpoint was the total amount of regular insulin infused. Secondary endpoints included glucose concentration mean, standard deviation (STD), maximum, and minimum value; and episodes of hypoglycemia (<70 (mg/dl)).

**Data and statistical analysis**
Using a numerical model of stress hyperglycemia,[9‑11] the number of participants that should be included to detect a difference in the total amount of insulin infused between the trial arms, and to reject the null hypothesis with a power of 90% and associated type I probability error of 0.05, was estimated to be of order 12.[2] The one-tailed Wilcoxon ranked test was used to analyze the primary outcome since the results from the numerical study have shown that IGF will lower total insulin requirements.[2] For secondary endpoints, a two-tailed test was used. For all endpoints,
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P < 0.05 was considered statistically significant. Finally, 95% confidence intervals (CIs) and effect sizes were calculated for significant endpoints.

Nonnutritional calorie sources
Calories from medication lipid suspensions and dextrose carriers were included in total calorie calculations.

RESULTS

Twenty-six patients were enrolled, five did not complete the protocol (they were liberated from the ventilator, including removal of the gastric feeding tube); another five patients never required an insulin infusion. Sixteen patients successfully completed the trial: 13/3 received CGF/IGF first. One patient was removed from the analysis because their liver failure inserted bias into the results. Patient characteristics are summarized in Table 1.

Trial outcomes
The primary outcome was the total amount of insulin infused, and it was lower in the IGF arm: \( P = 0.027 \) with effect size \( d = 0.6 \). In particular, 11 of 15 patients had a lower insulin requirement following IGF; this lowered the insulin infusion, on an average, by 1.4 U/patient/h. If the patient with liver failure was included in the trial data, the average total amount of insulin infused would be an additional 0.8 U/h/patient less in the IGF arm; removing this patient from the analysis was done post hoc. Table 2 contains a summary of the primary and secondary outcomes (with their associated \( P \)-values and CIs), and the total insulin infused data for all patients is presented in Figure 2.

Nonnutritional calorie sources
There was no difference in the calories delivered between trial arms: CGF \( (29.11 \pm 3.87 \text{ kcal/kg/day}) \) and IGF \( (28.45 \pm 4.94 \text{ kcal/kg/day}) \), \( P = 0.116 \) through Student’s \( t \)-test used because of several matched pairs.

Insulin infusion compliance
The insulin infusion compliance rate was similar between both trial arms: 92.2% (CGF) and 93.75% (IGF), \( P = 0.760 \) through Student’s \( t \)-test used because of several matched pairs.

Glucose concentration measurements
Blood specimens were arterial/venous in 11/4 of patients.

Complications
All patients completed data acquisition within 12 consecutive hours because none of the patients had FI. One patient had hypoglycemia, glucose concentration 67 (mg/dl); this occurred in the IGF arm for the patient with liver failure.

Table 1: Patient characteristics that completed trial

| Characteristic                  | Count (%) |
|--------------------------------|-----------|
| Male, n (%)                    | 9 (56.3)  |
| Age, mean ± STD                | 70.4 ± 12.6 |
| Apache, mean ± STD             | 17.9 ± 4.2 |
| BMI (kg/m\(^2\)), mean ± STD   | 28.1 ± 6.8 |
| Main ICU admission diagnosis, n (%) |          |
| Acute mental status change     | 2 (12.5)  |
| Liver failure                  | 1 (6.25)  |
| Pericarditis                   | 1 (6.25)  |
| Respiratory failure            | 10 (62.5) |
| Septic shock                   | 1 (6.25)  |
| Seizure                        | 1 (6.25)  |
| Comorbidity, n (%)             |           |
| Obesity                        | 9 (56.3)  |
| Type 1 diabetes mellitus       | 0 (0)     |
| Type 2 diabetes mellitus       | 10 (62.5) |
| Chronic pulmonary disease      | 7 (43.8)  |
| Preadmission dialysis          | 0 (0)     |
| Chronic liver disease          | 1 (6.25)  |
| Major interventions, n (%)     |           |
| Mechanical ventilation         | 16 (100)  |
| Low-dose vasopressors          | 6 (37.5)  |
| Renal replacement therapy      | 1 (6.25)  |
| Steroids                       | 6 (37.5)  |

ICU: Intensive care unit, BMI: Body mass index, STD: Standard deviation

Figure 2: Total insulin infused per patient. The patients have been reordered so that the difference between insulin infused for continuous gastric feeds (CGF) and intermittent gastric feeds (IGF) increases from left to right; for the first four patients total insulin was greatest in the IGF arm; otherwise, the CGF arm had the largest value.

DISCUSSION

To our knowledge, this is the first trial to compare the effects of IGF and CGF on glucose-insulin dynamics in critically ill medical patients who require an insulin infusion to maintain glucose concentrations between 140 and 180 (mg/dl): Our main result is that IGF decreases insulin requirements as compared to CGF.

Continuous enteral feeding has been linked to intestinal, hepatic, and gallbladder dysfunctions, a decrease in splanchnic blood flow, and a reduced ability to maintain muscle mass. Despite these concerns, it has remained the most common type of nutrition used in critically ill patients.

In general, the effects of IGF on ICU glucose dynamics are poorly understood. In the ICU, 20%–80% of patients suffer from stress hyperglycemia; although some patients may have occult diabetes. The disease alters...
glucose dynamics through several complex mechanisms and has been associated with increased mortality, particularly if not treated optimally. The ideal therapy,[14] would minimize glucose variability,[15] hyperglycemia,[16] and hypoglycemia[17] because all three metrics (measures of dysglycemia) have similar mortality risks.[18] It is, therefore, important to better understand how IGF affects dysglycemia measures because patient outcomes could be affected.

The only randomized controlled study that examined glucose and insulin dynamics in detail involved 12 healthy controls.[11] In this setting, IGF (not CGF) produced the largest response in terms of insulin secretion, which lowered the mean glucose concentration. Whether a similar dynamic would be observed in a heterogeneous ICU patient cohort with stress hyperglycemia has remained an open question. It is a complicated disease driven by several processes: Elevated hepatic gluconeogenesis,[19] increased insulin resistance,[20] decreased insulin secretion,[21] and increased renal excretion of insulin.[22] These pathologies combine to form a heterogeneous disorder that can make glucose dynamics sensitive to changes in nutritional[9,10] and insulin infusion[22] rates of administration, increasing patient glucose variability.

**Primary outcome:** Decreased total insulin requirement

When healthy adults are fed with IGF rather than CGF, it has been shown that the pancreas meets the absorption of a gastric nutrient “bolus” with a surge of insulin; the secreted insulin peaks rather quickly, on the order of 30–45 min. This efficient pancreatic response in healthy adults maintains glucose concentrations within a fairly tight range. A similar response to a food “bolus” was demonstrated to be present in critically ill virtual patients with stress hyperglycemia.[2] We posit that a similar mechanism may be the cause for the decrease in total insulin after IGF that was observed here; however, exogenous insulin levels should be measured in a future study for confirmation. There are two mechanisms in critical illness that can cause hypoinsulinemia: (1) attenuation of pancreatic insulin secretion, observed particularly in the critically ill elderly population, and (2) increase in the renal clearance of insulin.[21] Within the context of critical illness, it would appear that the pancreas can still mount an insulin surge in response to a food “bolus” that effectively reduces the insulin requirements associated with critical illness, using 140–180 (mg/dl) as the glucose concentration goal. This may be clinically relevant, as a retrospective study has identified intravenous insulin as an independent risk factor for ICU mortality.[23]

**SECONDARY OUTCOMES: DYSGLYCEMIA**

Metrics of dysglycemia, such as glucose variability,[15] hyperglycemia,[16] and episodes of hypoglycemia,[17] were chosen because they have been associated with poor ICU patient outcomes. Glucose variability, for example, is caused by fluctuations in glucose concentrations that can produce rapid changes in plasma osmolality that enhance cellular oxidative stress;[24] this may result in increased organ dysfunction[25] and may underpin the vasoconstriction, microvascular thrombosis, and inflammation that has been associated with elevated glucose variability.[26] Although there is no standard definition of glucose variability,[27] the association between glucose variability elevation and mortality is robust and appears to be independent of the calculation method. In this trial, standard deviation was chosen as the method to calculate glucose variability.

Insulin resistance is an important cause of stress hyperglycemia, and it increases the sensitivity of the glucose-insulin axis to perturbation from exogenous glucose concentration changes.[28] This dynamic can enhance “swings” in a patient’s glucose concentration if: (1) the patient’s nutritional rates are changed abruptly[2,10] and (2) if the exogenous insulin concentrations vary suddenly.[11,12] One could then speculate that, in the presence of stress hyperglycemia, IGFs may worsen maximum glucose (or hyperglycemia) and glucose variability, particularly if the patient is being treated with an insulin infusion based solely on hourly glucose concentration checks.[29] This concern follows from glucose absorption studies that have demonstrated that glucose concentrations peak quickly (in approximately 45 min in a healthy adult) following a food “bolus.”[30]

**Table 2: Means of primary and secondary outcomes values associated with continuous gastric feeds and intermittent gastric feeds, standard deviation of outcomes, associated P-values, and confidence interval for the significant measures**

| Outcomes                      | CGF Mean ± STD | IGF Mean ± STD | P    | 95% CI     |
|-------------------------------|----------------|----------------|------|------------|
| Total insulin infused (U)     | 15.07 ± 9.77   | 9.49 ± 9.06    | 0.027| 0.12-11.14 |
| Mean glucose (mg/dl)          | 182.71 ± 31.04 | 173.25 ± 37.61 | 0.084|            |
| Minimum glucose (mg/dl)       | 149.53 ± 28.20 | 142.33 ± 29.48 | 0.015| – 18-32.4  |
| Maximum glucose (mg/dl)       | 209.67 ± 32.18 | 198.00 ± 49.15 | 0.138|            |
| STD (mg/dl)                   | 24.82 ± 10.10  | 22.42 ± 12.13  | 0.689|            |
| Hypoglycemic episodes         | 0 ± 0          | 0 ± 0          | 1.0  |            |

The patient with liver failure has been excluded; thus, the total number of patients included for analysis was 15. CCF: Continuous gastric feed, IGF: Intermittent gastric feed, STD: Standard deviation, CI: Confidence interval
If this rapid increase in glucose absorption is present in an ICU population receiving IGF (as an infusion over 60 min), then the inherent time lag associated with an insulin infusion that is only able to rate adjust hourly may result in an increase in the maximum glucose concentration and glucose variability.

For these reasons, it was an unexpected finding that IGF did not adversely alter the dysglycemia metrics studied. Within the context of dysglycemia, IGF and CGF can likely be viewed as being equally safe, although larger studies are required to confirm this assertion.

**Trial limitations**

**Small patient cohort**

Although the total amount of insulin infused in the IGF arm was statistically smaller, the CI lower bound was close to zero: The insulin decrease may, therefore, not be clinically significant despite effect size \( d = 0.6 \). A larger study could address this concern, as well as provide greater power for the glucose concentration metrics.

**Patient withdrawal**

Patients’ partial recovery from stress hyperglycemia could account for the lower insulin requirement in the IGF arm, as only three patients received IGF first; asymmetry was created by a patient withdrawal within the trial. However, the time between data collection periods was only 4 h: this time interval seems too short to allow for a partial recovery with sufficient magnitude to account for the observed decrease in insulin infused. We are unaware, however, of any literature to support such a claim. Note, the three patients who received IGF first still had a lower insulin requirement.

**Rapid clinical deterioration**

One patient who deteriorated rapidly from liver failure may have introduced a bias into the results; they transitioned from a high insulin infusion requirement (CGF arm) to no insulin requirement (IGF arm) during the crossover. Removing this patient from the analysis did not change any conclusions, but the CI for the endpoints were widened. Liver failure should have been an exclusion criterion.

**Glucose concentration measurement error**

The majority of patients in this trial had their glucose concentrations measured with a RAPIDpoint©. According to the International Organization for Standardization, measurements shall fall within ±15 (mg/dl) of the results of the manufacturer’s measurement procedure at glucose concentrations <75 (mg/dl) and within ±20% at glucose concentrations ≥75 (mg/dl).\(^{[31]}\) A larger clinical study would be required to mitigate an unintentional bias caused by glucose measurement uncertainty.

**Insulin infusion compliance**

Compliance with the insulin infusion protocol occurred 92.2% of the time in the CGF arm and 93.75% of the time in the IGF arm. A two-tailed \( t \)-student demonstrated that these distributions were statistically similar, \( P = 0.741 \); however, the small cohort size may still have allowed bias to alter the trial results.

**Absorption of enteral nutrition was not measured**

All patients proceeded through the protocol without FI, it was, therefore, assumed that nutritional absorption would be the same between the trial arms; however, future studies should consider measuring glucose absorption to avoid having to make this assumption.

**CONCLUSIONS**

This pilot trial has demonstrated that critically ill medical patients who require an insulin infusion to maintain glucose concentrations between 140 and 180 (mg/dl) may have a lower insulin requirement when fed with IGF, not CGF; metrics of dysglycemia were similar. A larger clinical trial should be done to confirm these findings, and improve measurement precision and statistical power before a recommendation can be made.

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**Conflicts of interest**

There are no conflicts of interest.

**Research Quality and Ethics Statement**

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network, namely the Consolidated Standards of Reporting Trials (CONSORT) statement for pilot randomized controlled trials.\(^{[32]}\) This study was approved by the Institutional Review Board / Ethics Committee at the San Antonio Military Medical Center (IRB #C.2016.143) and was registered with Clinicaltrials.gov (identifier NCT02853799). The views expressed are those of the authors and do not reflect the official policy or position of the Department of the Air Force, the Department of the Army, the Department of Defense, or the US Government.
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