Continuous versus bolus tube feeds: Does the modality affect glycemic variability, tube feeding volume, caloric intake, or insulin utilization?

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ABSTRACT

Introduction: Enteral nutrition (EN) is very important to optimizing outcomes in critical illness. Debate exists regarding the best strategy for enteral tube feeding (TF), with concerns that bolus TF (BTF) may increase glycemic variability (GV) but result in fewer nutritional interruptions than continuous TF (CTF). This study examines if there is a difference in GV, insulin usage, TF volume, and caloric delivery among intensive care patients receiving BTF versus CTF. We hypothesize that there are no significant differences between CTF and BTF when comparing the above parameters.

Materials and Methods: Prospective, randomized pilot study of critically ill adult patients undergoing percutaneous endoscopic gastrostomy (PEG) placement for EN was performed between March 1, 2012 and May 15, 2014. Patients were randomized to BTF or CTF. Glucose values, insulin use, TF volume, and calories administered were recorded. Data were organized into 12-h epochs for statistical analyses and GV determination. In addition, time to ≥80% nutritional delivery goal, demographics, Acute Physiology and Chronic Health Evaluation II scores, and TF interruptions were examined. When performing BTF versus CTF assessments, continuous parameters were compared using Mann–Whitney U-test or repeated measures t-test, as appropriate. Categorical data were analyzed using Fisher’s exact test.

Results: No significant demographic or physiologic differences between the CTF (n = 24) and BTF (n = 26) groups were seen. The immediate post-PEG 12-h epoch showed significantly lower GV and median TF volume for patients in the CTF group. All subsequent epochs (up to 18 days post-PEG) showed no differences in GV, insulin use, TF volume, or caloric intake. Insulin use for both groups increased when comparing the first 24 h post-PEG values to measurements from day 8. There were no differences in TF interruptions, time to ≥80% nutritional delivery goal, or hypoglycemic episodes.

Conclusions: This study demonstrated no clinically relevant differences in GV, insulin use, TF volume or caloric intake between BTF and CTF groups. Despite some shortcomings, our data suggest that providers should not feel limited to BTF or CTF because of concerns for GV, time to goal nutrition, insulin use, or caloric intake, and should consider other factors such as resource utilization, ease of administration, and/or institutional/patient characteristics.

Key Words: Continuous tube feeding, enteral nutrition, glycemic variability, intermittent tube feeding, percutaneous endoscopic gastrostomy, tube feeding
INTRODUCTION

Enteral nutrition (EN) in the Intensive Care Unit (ICU) is critical to good patient outcomes. Enteral provision of caloric intake favorably modulates disease severity,[1,2] immune system function,[3] gastrointestinal integrity,[4] and mucosal host defenses.[5,6] EN can be given as intermittent (bolus tube feeding [BTF]) or continuous tube feeding (CTF).[7,8] BTFs are given at standard intervals, allow greater patient mobility and are considered to be more physiological with regards to the cephalic phase of digestion and gut homeostasis.[9,10] CTFs are thought to be better tolerated by patients with the limited absorptive gut surface area or gastrointestinal dysfunction but are associated with more tube clogging and require the patient to be attached to an infusion pump for significant periods of time.[8,11] It has been suggested that CTFs may provide better glucose control when compared to BTFs.[12] Despite significant interest and controversy, there are only limited data on the effect of BTF versus CTF on key parameters pertaining to EN administration, including glycemic variability (GV).[13]

Since Van den Berghe et al.[14] published their seminal work on the association between glycemic control and improved outcomes in surgical patients there has been a proliferation of protocols incorporating the intensive insulin therapy paradigm.[15-18] Subsequent to the early reports, it has been increasingly recognized that GV, and not the glucose levels alone, correlates with increased mortality independent of hypoglycemia, presence of diabetes, organ dysfunction, or treatment.[19-21] GV is an objective measure of glucose fluctuations[20-22] with previous studies showing that acute glucose gyrations may induce endothelial cell damage, apoptosis, and could be associated with worse clinical outcomes.[23,24] The primary objective of this study was to determine if there is a difference in GV and insulin utilization among critically ill patients receiving BTF versus CTF via percutaneous endoscopic gastrostomy (PEG) tube. Secondary objectives included comparisons of tube feed volume and caloric delivery, the incidence of hypoglycemia as well as the time needed to achieve “≥80% goal nutrition.” We hypothesized that there will be no significant differences in the above parameters between BTF and CTF groups.

MATERIALS AND METHODS

This is an Institutional Review Board approved, prospective, randomized pilot study conducted in both surgical and neurologic critical care units at a single institution. During the period from March 2012 to May 2014, a total of 50 patients were enrolled. Inclusion criteria included: (a) Admission to the ICU; (b) age ≥18 years and ≤89 years; (c) planned placement of PEG tube during current ICU admission; and (d) attainment of informed consent. Exclusion criteria included patient age <18 or >90, contraindication to PEG tube, prisoner status, as well as pregnancy.

After consent for PEG tube placement was obtained for patients who independently met indications for longer-term enteral access, a notification was sent to the clinical research team so that each patient could be evaluated for possible inclusion in the study. The patient or patient’s representative provided consent for enrollment, followed by patient randomization to receive either BTFs or CTFs once PEG tube placement occurred. All TFs were begun within 24 h of PEG device placement.

Primary objectives of this study were to determine the impact of EN regimen (intermitted versus continuous) on GV and insulin utilization. Secondary outcomes included the incidence of hypoglycemic episodes (glucose measurements ≤75 mg/dL), TF volume, total caloric intake, and median time to ≥80% of TF goal rate (as determined independently by the clinical nutrition service prior to PEG placement), as well as TF interruptions (e.g., tube feed holds prior to planned operating room procedures, episodes of TF intolerance as determined by nursing). Additional variables collected included TF formula types and caloric densities, patient demographics (age and gender), the Acute Physiology and Chronic Health Evaluation (APACHE) II scores, Simplified Acute Physiology Score (SAPS) II, and the Glasgow coma scale (GCS).

Traditionally, GV has been presented using various methods including (a) Standard deviation[25] (b) mean daily change in serum glucose (i.e., mean difference between daily maximum and minimum glucose values); (c) the glucose lability index as well as the mean amplitude of glycemic excursion technique.[26] A variation on the “mean daily change” has been previously presented by our group[20] and is called “the glucogram.”[27,28] Here, an epoch-based financial chart is constructed that utilizes the “open-high-low-close” (OHLC, Figure 1) paradigm.[27,28] These measurements are then organized into 12-h epochs, and GV is subsequently calculated by determining serial differences between the maximum and the minimum value for each standardized time period.[20,28]

To assess the effect of TF modality (BTF versus CTF) on GV and insulin utilization in patients following PEG tube placement, serial (i.e., formal serum and point-of-care fingerstick testing) glucose determinations were obtained in real-time. Raw glucose measurements were recorded over a range of time frequencies (from 60 min to 8 h) for each patient’s ICU stay. These measurements were then compressed into an equal, standardized 12-h epochs and formatted into the OHLC paradigm.[29] For each epoch, the opening value (the first value in the epoch), the minimum and maximum values, and the closing (last)
value were recorded for analysis. GV was defined as the difference between maximum and minimum value.

All patients in the surgical and neurological ICU at our center are placed on an insulin sliding scale regimen administered every 6 h for the treatment of blood glucose values >120 mg/dL. A continuous insulin infusion may be initiated if a patient has two consecutive blood glucose values >200 mg/dL or at the discretion of an intensivist in the setting of persistent hyperglycemia. The insulin infusion protocol is nursing-driven and is titrated hourly based on the current and previous blood glucose values, with a goal range of 110–150 mg/dL. Blood glucose values for the BTF group were measured, whenever possible, before bolus feeds were given. The total number of units of insulin administered during each epoch was also recorded.

The study was designed to detect a mean difference of 25% in our primary endpoints (GV and insulin use) with power of 0.80 and alpha <0.05. To achieve this objective, we need approximately 25 patients in each study group. Primary analyses for GV, EN volume, insulin utilization, and caloric intake between BTF and CTF were performed using repeated measures t-test. Additional comparative analyses were performed for age, gender, APACHE II, SAPS II, and GCS scores, median time to goal ≥80% nutrition, number of 12-h epochs, and incidence of hypoglycemia using Mann–Whitney U-test, Student’s t-test, and Fisher’s exact test.

**RESULTS**

Baseline characteristics for the BTF and CTF groups are presented in Table 1. Fifty patients were enrolled in the study. No patients died during the active study period (i.e., up to 18 days post-PEG). There were no statistical differences in age, gender, APACHE II scores, SAPS II scores, GCS scores, body mass index, or a number of 12-h epochs per patient. There were no statistical differences in the secondary outcomes of median time to ≥80% goal nutrition, TF interruptions, and incidence of hypoglycemia (≤75 mg/dL). The distribution of various tube feed formulae as well as their corresponding caloric densities are outlined in Table 2.

![Figure 1: Schematic representation of the open-high-low-close “bar graph” paradigm used to compress data in this study into standardized 12-h epochs](image)

Except for the initial 12-h epoch, there were no differences in GV for the 34 study epochs between the BTF and CTF groups [Figure 2]. Similarly, there were no statistical differences in insulin use between the two groups [Figure 3]. In order to help determine whether physiologic acuity may have played a role in GV for either of the groups, daily APACHE II scores were compared for BTF and CTF groups, with no statistical differences noted [Figure 4].

When examining the aggregate data for combined groups, GV decreased over time, such that the GV during the first epoch was significantly greater than that from the last epoch \( (P < 0.05, \text{Figure 5}) \). Likewise, for combined groups, insulin use significantly increased towards the mid-point of the data analysis period (17th epoch) and then decreased toward the final recorded period (34th epoch, \( P < 0.05, \text{Figure 5} \)).

Finally, when examining the two groups for TF volume and caloric intake, no significant differences were noted, with the exception of the mean TF volume that was higher for the BTF group during the very first monitoring epoch [Figure 6]. Interestingly, data for the corresponding epoch shows no difference in the mean caloric intake, likely representing different caloric densities of the early feeds.

![Figure 2: Composite graph of glycemic variability for bolus (black line, \( n = 26 \)) and continuous (red line, \( n = 24 \)) groups. Except for the initial epoch (indicated by *), no statistical differences were seen between the two groups. Data presented as mean ± standard error](image)

**Table 1: Demographics and descriptive characteristics of the bolus and continuous tube feed groups**

| Category                              | Bolus  | Continuous |
|---------------------------------------|--------|------------|
| Number of patients                    | 26     | 24         |
| Age (mean ± SD)                       | 59.2 ± 17.8 | 60.0 ± 20.6 |
| Gender (male:female)                  | 17:9   | 14:10      |
| APACHE II (mean ± SD)                 | 14.0 ± 4.37 | 14.6 ± 4.26 |
| SAPS II (mean ± SD)                   | 10.4 ± 2.65 | 9.95 ± 2.65 |
| Preexisting diabetes (n, %)           | 6 (23.1) | 4 (16.7)   |
| BMI, mean ± SD                        | 30.7 ± 8.1 | 30.5 ± 8.6 |
| Median time to ≥80% goal nutrition (mean ± SE) | 24 h (12–192) | 24 h (12–84) |
| Number of 12-h epochs                 | 353 (13.5 per patient) | 362 (15.1 per patient) |
| Tube feeding interruptions (per number of epochs) (%) | 21/353 (5.95) | 24/362 (6.63) |
| Incidence of hypoglycemia (≤75 mg/dL per number of epochs) (%) | 10/353 (2.83) | 14/362 (3.87) |

None of the differences are statistically significant. BMI: Body mass index, SD: Standard deviation, APACHE: Acute Physiology and Chronic Health Evaluation, SAPS: Simplified Acute Physiology Score, SE: Standard error.
DISCUSSION

This prospective, randomized pilot study provides evidence to support the hypothesis that the choice of BTF versus CTF administration does not significantly affect GV. Furthermore, we also found that there was no significant difference in overall insulin utilization between the two groups [Figure 3]. Despite some evidence suggesting that CTF may result in improved glucose control in enterally fed patients,\textsuperscript{15} our data are generally consistent with previous observations that other factors, such as the carbohydrate TF content and proper synchronization of EN schedule with insulin/glucose-lowering agent administration may be much more important as determinants of optimal glycemic control.\textsuperscript{30,31} Although much remains to be learned about the relationship between CTF versus BTF and a number of modulators of the physiologic response following food intake (e.g., ghrelin),\textsuperscript{32,34} there is some evidence that the secretion of trophic gut peptides is not significantly different in bolus versus continuous feeding.\textsuperscript{34}

We observed no significant differences in the median time to achieve ≥80% goal nutrition between BTF and CTF groups. This is an important finding that further highlights the importance of maintaining clinical focus on ensuring that adequate caloric intake is achieved, as opposed to an emphasis on a specific mode of delivery. At the same time, there is evidence to suggest that

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**Table 2: Tube feed types utilized for the bolus and continuous tube feed groups**

| Tube feed type (Cal/mL) | Bolus | Continuous |
|-------------------------|-------|------------|
| Glucerna (1.2)          | 4     | 3          |
| Impact (1.5)            | 9     | 9          |
| Jevity (1.2)            | 4     | 5          |
| Nepro (1.8)             | 2     | 2          |
| Peptamen (1.5)          | 2     | 2          |
| Perative (1.3)          | 3     | 3          |
| Pivot (1.5)             | 2     | 1          |
| Totals                  | 26    | 24         |

Calories per unit of tube feed volume are provided in parentheses; Glucerna, Jevity, Nepro, Perative & Pivot (Abbott Laboratories, Columbus, Ohio, USA); Impact & Peptamen (Nestle Health Science, Florham Park, New Jersey, USA)

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![Figure 3: Composite graph of insulin utilization for bolus (black line, n = 26) and continuous (red line, n = 24) groups. No statistically significant differences were found. Data presented as mean ± standard error](image1)

![Figure 4: Composite graph of daily Acute Physiology and Chronic Health Evaluation II scores. Black line represents the bolus group (n = 26) whereas red line represents the continuous group (n = 24). None of the differences are statistically significant. Data presented as mean ± standard error](image2)

![Figure 5: Composite graphs of insulin use (top right) and glycemic variability (bottom left) for combined groups. Red solid line indicates mean value whereas dotted black line indicates a 2-epoch moving average. Of note, insulin use increased significantly between the early epochs (1st–3rd) and the middle (15th–18th) epochs. Glycemic variability decreased over time](image3)

![Figure 6: Composite graphs of mean tube feed volumes (top) and caloric intake (bottom) for the two groups. Black line represents the bolus group (n = 26) whereas red line represents the continuous group (n = 24). The only statistically significant difference is seen for the initial epoch for the mean tube feeding volume (indicated by *), with no significant differences noted thereafter. Data presented as mean ± standard error](image4)
certain patient populations may be able to achieve nutritional goals earlier with the use of CTF. These groups include brain-injured patients and adult burn victims. Of interest, our data demonstrate no difference in the total percentage of epochs with interruptions in EN administration between the two study groups [Table 1].

Because this report focused on GV and not glucose levels per se, this study did not differentiate patients according to the baseline presence or control of diabetes mellitus. Instead, the authors approached serum glucose measurements are a “barometer” of physiologic stress and a global reflection of the body’s ability to maintain homeostasis. In this context, TF modality was only one of the possible factors influencing serum glucose concentrations. Despite that, the authors believed that if there were indeed “systemic physiologic differences” between patients receiving BTF and CTF, these effects would still be manifest in the global composite representation of GV differences between the two groups. Although a variety of events are known to modulate GV in acutely ill patients, the fact that our study demonstrated no significant differences in APACHE II scores between the two groups across the entire spectrum of temporal measurements [Figure 4], indicates that baseline physiologic differences are unlikely to play a dominant role in affecting GV when composite data are compared side-by-side. Another factor that lends further credence to the authors’ assumptions is the observation that the two groups had similar composite insulin requirements throughout the global observation period [Figure 3]. Further research in this area is warranted, and should include multi-variable assessment of factors related to both GV and physiologic stress. In the current study, mean TF volume and caloric intake, as measured every 12 h, were similar for both the CTF and BTF groups [Figure 6]. This is consistent with the findings of Serpa et al., who found that despite slightly greater enteral input in patients receiving CTF during the initial 24 h, there were no significant differences in nutritional administration between the CTF and BTF groups beyond this early period. Similar to Ciocon et al., the current study did not demonstrate clinically significant differences between caloric delivery in CTF and BTF groups. This finding further corroborates the authors’ perception that the tube feed administration modality is not a factor of greatest importance, and it may be more critical to minimize TF interruptions, optimize TF formula composition, and ensuring that sufficient volume of the desired formula is reliably delivered.

The observed decrease in GV over time in both groups [Figure 5] is likely attributed to the resolution of critical illness, a finding that is also supported by the down-trending APACHE II scores for both study groups [Figure 4]. The initial increase and the subsequent peak in insulin utilization [Figure 3 and 1st-17th epochs], followed by a decrease in insulin use [Figure 3 and 18th-34th epochs] may be attributable to a number of factors such as corresponding changes in illness severity, fewer acute events (i.e., sepsis, hemorrhage). and/or more closely adherent glucose protocol implementation by nursing. Related to the latter two points, the current study provides no evidence that either BTF or CTF are associated with greater incidence of hypoglycemia (≤75 mg/dL, Table 1). In the current era of value-based healthcare, focus has been placed on providing quality patient care while being mindful of resource utilization and patient satisfaction. BTFs have been suggested by some to be less burdensome than CTFs, including considerations such as the cost of a continuous infusion pump, increased mobility and the ability to participate in physical therapy, which may lead to shorter hospitalizations and lower morbidity. Consequently, when considering the TF delivery approach, it may be optimal for practitioners to focus on personalized, case-by-case determination of what methodology to employ. For example, a hypothetical patient may be placed on CTF during the acute illness, followed by transition to BTF during the convalescent and rehabilitation phases.

Limitations of this study include its relatively small sample size, lack of strict patient inclusion/exclusion criteria based on diagnoses or preexisting conditions (e.g., the presence of diabetes or active corticosteroid use), as well as possible variability in overall clinical approaches during the 2 years of study enrollment period. In addition, both study groups (BTF and CTF) decreased in size between the original set of measurements (1st epoch) and the final set of measurements (34th epoch). Thus, our GV data may have become more biased for the more temporally distant epochs. In addition, our study focused exclusively on patients undergoing PEG tube placement. Consequently, these findings may not be translatable to patients with other enteral access methods, or those in other healthcare settings. Finally, acute events during each patient’s hospitalization were not analyzed in the context of low-level GV trends detectable using the more sensitive financial “momentum” or stochastic indicators. Such acute events may include early sepsis or end-organ failure, with known clinical correlations between increased GV and worse clinical outcomes under certain pathophysiologic conditions. Strengths of this report include the novel and unique character of information presented, the original analytic approaches, and the much needed answers to clinically relevant questions regarding enteral feeding administration modalities.
CONCLUSIONS

The choice of CTF versus BTF approach does not affect GV or insulin utilization. In addition, there does not appear to be a difference in median time to ≥80% goal nutrition and incidence of hypoglycemia (≤75 mg/dL) between BTF and CTF groups. Despite some shortcomings, our data suggest that providers should not feel limited to either type of feeding modality because of concerns for GV or insulin usage and should consider other factors such as resource utilization, ease of administration, or institution/unit- and patient-specific considerations.

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Conflicts of interest

There are no conflicts of interest.

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