Cycled total parenteral nutrition: is it more effective?\textsuperscript{1,2}

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Since the introduction of total parenteral nutrition (TPN) by Dudrick et al\textsuperscript{1} (1) and Wilmore\textsuperscript{2} (2), the standard technique in the United States has been continuous infusion of hypertonic dextrose and amino acids into a central vein. This has proven to be an important therapeutic advance in the care of critically ill patients. In addition, the use of TPN has allowed a small subset of patients with extreme short bowel syndrome to survive for many years in the absence of a gastrointestinal tract capable of absorbing adequate nutrients for survival.

Despite many advantages, feeding into the central circulation is clearly nonphysiologic. There are many reasons why parenteral feeding is significantly different from enteral feeding, but the most obvious is the continuous nature of the feeding. The human body has developed an elegant system to store nutrients so that energy balance is not necessary on a minute-to-minute basis. This allows us to eat intermittently because we are capable of mobilizing the necessary micro- and macronutrients during the postabsorptive state. This mobilization of energy and nutrients, however, requires a hormonal milieu of low serum insulin characteristic of the postabsorptive state. With the use of continuous feeding, the body remains in a high-insulin, fed state with the tendency to store nutrients instead of mobilizing them\textsuperscript{3}. This alteration in normal physiology has led to the concern that it may be possible to develop nutritional deficits despite adequate feeding\textsuperscript{4}.

Especially high insulin concentrations are maintained with the use of continuous hypertonic dextrose\textsuperscript{3, 5, 6}. This results in two important physiologic phenomena. First, high insulin concentrations promote a lipogenic state. Therefore, when adequate energy is provided, some of the dextrose is converted to fat, especially in the liver, the primary site of de novo lipogenesis\textsuperscript{3}. This can lead to fatty infiltration of the liver and the subsequent increase in liver transaminases associated with liver damage if excess energy is given. Furthermore, by limiting peripheral lipolysis, serum fatty acids fall, depriving the body of an important fuel source as well as the essential fatty acid linoleic acid, which is stored in abundance in adipose tissue but cannot be as easily mobilized in this hormonal environment\textsuperscript{4, 6}. Second, a high-insulin state promotes the peripheral utilization of amino acids in skeletal muscle, potentially depriving the vital organs of the amino acids necessary during acute illness when inadequate exogenous amino acids are provided. This is in stark contrast with the normal physiologic response to stress, in which the body mobilizes endogenous amino acids from skeletal muscle in order to support the vital visceral protein pool.

To combat the theoretical problems associated with continuous hypertonic dextrose, investigators began experimenting with cycled TPN during the 1970s\textsuperscript{6, 7}. In these early studies, dextrose was provided in a cycled fashion, whereas amino acids or saline were provided continuously. As expected, serum glucose concentrations decreased by nearly 30% and serum insulin concentrations by 60%. In addition, serum fatty acid concentrations rose, indicating greater peripheral lipolysis. Interestingly, there was an associated decrease in liver-associated transaminases and alkaline phosphatase activity. Many patients had resolution of hepatomegaly, and in one case report, serial liver biopsies showed complete reversal of the fatty liver changes after several weeks of cycled TPN\textsuperscript{6}. These changes were presumably due to the low-insulin, dextrose-free periods, during which the body was capable of both mobilizing the fat in the liver as well as limiting lipogenesis, thereby minimizing fatty infiltration and its associated liver damage.

In addition, these studies showed a minimal improvement in serum albumin concentrations\textsuperscript{7}. This suggested better visceral protein preservation because the infused amino acids may have been less likely to be utilized by skeletal muscle during the low-insulin, dextrose-free periods.

Mascioli et al\textsuperscript{4} showed essential fatty acid deficiency (EFAD) in patients receiving continuous, fat-free TPN. In his study, five of five patients on continuous, fat-free TPN had biochemical evidence of EFAD after 2–6 wk. Two patients receiving cycled TPN did not develop EFAD even after 6 wk. Furthermore, one of the patients showed reversal of EFAD after 1 wk of cycled TPN. The human body, of course, has large fat stores, 10% of which are the essential fatty acid linoleic acid. With these stores EFAD should not develop for several months or more. Despite large quantities of linoleic acid, this essential nutrient could not be mobilized during the high-insulin state associated with continuous feeding. With the use of cyclic TPN, lipolysis was stimulated during the dextrose-free periods, resulting in sufficient mobilization of linoleic acid to prevent and even reverse EFAD.

In this month’s issue, Morimoto et al\textsuperscript{8} provide additional evidence that cycled TPN aids in the preservation of visceral protein synthesis. Using the elegant techniques of molecular

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biology, they have provided evidence that cycled TPN increases the level of albumin mRNA and thereby its synthetic rate. This clearly shows that the method of TPN administration can have a profound effect, affecting even the transcriptional regulation of protein synthesis.

Although Morimoto et al’s work is quite convincing, it has a few flaws that should be addressed. First, to provide isenergetic and isonitrogenous feeding, it is necessary to provide dextrose and amino acids at twice the rate while providing cyclic TPN. Therefore, during the infusion, the cycled animals would have relatively more amino acids available, which can quickly alter the albumin synthetic rate (9). Because all of the animals were killed at the same time (2 h into the infusion for the cycled animals), it is possible that the results might have been skewed by the high rate of infusion when the animals were killed. This is certainly true for albumin synthetic rates, which are quickly altered by amino acid and energy availability (9). However, Morimoto et al measured mRNA levels directly, which have a slower turnover rate and are therefore more likely to represent albumin transcriptional activity over 24 h. Nevertheless, it may have been revealing to measure levels of mRNA and binding proteins during the fasting period as well. Furthermore, despite the significant difference in transcriptional activity shown in Morimoto et al’s work, the serum albumin concentrations were not significantly different between the cycled and continuous TPN groups. Although a difference may have been shown if the experiment had continued longer, as predicted by the authors, it is still uncertain whether these small biochemical changes result in any significant clinical change.

Is cycled TPN better than continuous infusion? Clearly, as outlined above and shown by Morimoto et al, cycled TPN does provide some benefits. By providing a period of fasting the body is capable of mobilizing fat, causing less fatty infiltration of the liver and EFAD. Secondly, there is some evidence that cycled TPN might be better at preserving visceral protein synthesis, although this has not translated into clinical benefits. Probably the most important benefit of cycled TPN has yet to be mentioned. It allows the convalescing patient ≤ 14 h of freedom from intravenous therapy, allowing for increased activity, which is both psychologically and physically beneficial. Thus, the preferred circumstance for cycled TPN would be in patients convalescing or at home. However, in critically ill, bedridden patients cycled TPN cannot be recommended. The purported benefits of cycled TPN have never resulted in significant clinical change and are therefore less likely to be of value in this population. In the critically ill population there are often multiple metabolic abnormalities, including electrolyte, acid-base, and water disturbances, all of which are easier and safer to stabilize with a continuous infusion. Furthermore, because of the insulin resistance associated with critical illness, these patients are less likely to tolerate the high dextrose loads associated with cycled TPN without marked and potentially harmful fluctuations in serum glucose concentrations, nor can they usually tolerate the high-volume load associated with the cycle. Therefore, despite the many benefits of cycled TPN for convalescent or stable patients, the benefits are not sufficient to recommend its use in those critically ill. In this population, continuous administration of TPN clearly remains the gold standard.

REFERENCES