ONE IF BY GUT AND TWO IF IV


Bozetti and his colleagues suggested that postoperative enteral nutrition might blunt potentially injurious systemic inflammatory and metabolic responses associated with parenteral nutrition. Under the auspices of the Italian Society for Parenteral and Enteral Nutrition, they undertook a large cooperative randomized controlled trial (RCT) to compare the 2 nutritional interventions in malnourished patients undergoing major cancer surgery.

The investigators performed a power calculation. Assuming that the parenteral nutrition group would have a 40% complication rate, and desiring to show that enteral nutrition reduced that rate to 25%, they estimated that they would have to include 150 patients in each arm. Between January 1997 and March 1999, they randomized 158/159 patients to parenteral/enteral nutrition, respectively. At the end of the trial, the patients who received postoperative parenteral nutrition had worse outcomes. The total complication rates in the parenteral/enteral groups were 49%/34% (P = 0.005). About a quarter of the complications in each group were major ones; although the trend remained favoring the enteral group, the actual rates (13%/9%) were not statistically significantly different (P = 0.207). The differences in the infectious complications (27%/16%) were significant (P = 0.018), whereas the differences in the noninfectious ones were not (36%/26%, P = 0.064).

The mortality rate tended to be higher, but not statistically significantly so, in the parenteral nutrition recipients (3.2% vs. 1.3%, P > 0.05). The postoperative length of stay was longer in the patients who received parenteral nutrition (15.0 vs. 13.4 days, P = 0.009).

The investigators separately classified “adverse events,” namely side effects attributable to the therapeutic interventions (gastrointestinal morbidity or enteral tube/intravenous catheter problems). These events were more common in the enteral nutrition recipients. Only 125 of the 159 patients randomized to enteral nutrition actually received at least 50% of the planned caloric intake; 14 of the remaining 34 patients were provided with parenteral nutrition as a fallback. All of the patients randomized to the parenteral nutrition arm received what the investigators believed to be adequate nutrient intake. The patients in the parenteral nutrition received larger caloric loads and their average blood glucose level was higher. (Hyperglycemia may be associated with an increased risk of infection [JPN J Parenter Enteral Nutr 1999;23:52].) The investigators separately assessed the frequency of complications in the patients who did, or did not, adhere to the planned enteral nutritional regimen. The rates of both infectious and noninfectious ones were lower in the 125 who tolerated the enteral infusions. Because those who tolerated the infusions had a better outcome, the investigators suggested that “a dose-response relation might exist.”

Two overall conclusions were reached. The first (and major) one was that early enteral nutrition significantly reduced the postoperative complication rates and length of hospitalization. The second was that parenteral nutrition was better tolerated.

Comment. There has been a long-standing debate about the relative values of providing nutritional support (a nonvolutral infusion of nutrient solutions) through the veins or directly into the gastrointestinal tract. Some of these studies have been reviewed here before (Gastroenterology 1993;105:299–300, 1997;113:1414–1415, 1998; 114:850–852, and 1998;115:1299–1301). Now an entire medical society has entered into the fray.

Before considering this work, it should be noted that 2 of the investigators, Drs. Braga and Gianotti, have previously conducted a trial that compared parenteral nutrition to 2 enteral nutrition formulations (a standard one and one that contains putative immunonutrients). This RCT, reflecting work carried out in the 1990s and also assessing the value of such nutritional support in cancer patients undergoing surgery, has been reported in several publications (Beitr Infusionsther Transfusionsmed 1995;22:280–284, Eur J Surg 1996;162:105–112, Arch Surg 1997;132:1222–1230, Crit Care Med 1998;26:24–30, Crit Care Med 2001;29:242–248). Each consecutive report seems to be describing the results after some more patients were added and/or assessing a different outcome. The study found that the parenteral nutrition was less effective than either of the 2 enteral nutritional interventions. At some time, the decision was made to extend the study only in patients with pancreatic cancer; those data, derived from both new and old patients, were presented early in 1999 (JPN J Parenter Enteral Nutr 1999;23:52). I mention all of this to point out that the current trial was being conducted within the same time frame. One cannot help but wonder if any of the patients in this Lancet article are also part of the Braga/Gianotti effort, which is not cited in the Lancet article. If the patients were all different and 2 separate trials were being conducted simultaneously, it is unclear how Drs. Braga and Gianotti made allocation decisions (i.e., which patients went into which study).

With this proviso, let us consider the conclusions of this study. Bozetti et al. asserted that enteral nutrition might be beneficial because of the “dose-response” effect. This assertion should be viewed critically. The study did not randomize patients to different amounts of nutrients (which would be the standard way to assess dose-response). Rather, the amount of nutrients received depended on the tolerance of the patient to the enteral infusions. It is incorrect simply to compare these 2 groups because such a maneuver assumes that the patients who received more enteral nutrition are comparable to those who received less. Clearly, there had to be some reason(s) why only some of the patients were intolerant. One alternate explanation for the observation is that sicker patients, who are more likely to have postoperative complications, are less likely to be tolerant of the nutrient infusion.

What about the second conclusion of the investigators? Does it help us clinically? The recipients of the enteral nutrition certainly had more side effects. In some of these patients, those side effects were so severe that the enteral nutrition had to be stopped. Thus, the average caloric intake by the enteral nutrition group was less than the average intake when the nutrition was delivered intravenously. However,
Despite receiving more calories, the parenteral nutrition group had a poorer outcome. In other words, the extra nutrient intake translated into clinical harm.

This latter observation leads us to the implications of the major conclusion, namely the precise utility of any nutritional support. The primary finding of this trial, that there were more complications in the recipients of the parenteral nutrition, agrees with the results of a recent meta-analysis (Am J Clin Nutr 2001;74:534–542). Such comparative study designs cannot provide any insight into the absolute value of either form of nutritional support. Treatment A may be better than treatment B, but both may be inferior to doing nothing. In this case, what if postoperative parenteral nutrition is harmful? If so, we would not know if enteral nutrition, even if less harmful, would be beneficial. What do we know about postoperative parenteral nutrition?

Tim Lipman, Sam Klein, and I recently published a systematic review of parenteral nutrition (Gastroenterology 2000;121:970–1001). We included 82 RCTs that compared parenteral nutrition to true control groups (those receiving no nutritional support). When the data from all 82 trials were combined, the only significant difference between treatment and no treatment that was found was that there were more infectious complications in the parenteral nutrition recipients. We then considered only the 41 perioperative RCTs. In this group of trials, no significant differences were found; however, because the confidence intervals overlapped zero for all of the calculations, we could not exclude the presence of a harmful effect even in this clinical situation. Furthermore, a previously published data-pooling exercise estimated that although preoperative parenteral nutrition reduced postoperative complications by 10%, postoperative parenteral nutrition did just the opposite. The use of the latter intervention resulted in an absolute increase in complications of 10% (JPN 1997;21:133–156). (In our analysis, the outcomes were slightly better when the nutrient infusion was used preoperatively rather than postoperatively, but none of the differences were statistically significant.)

This debate about enteral versus parenteral nutrition is intellectually interesting. However, it is difficult to apply the data in the clinical arena because we are unsure about the absolute value of either intervention (compared with doing nothing). Doing such comparative studies is analogous to erecting the second floor of a building before laying the foundation. Before we worry about whether a nonvolitional infusion of nutrients should be delivered into the gastrointestinal tract or the vein, we should clarify the circumstances under which we should be delivering such an infusion anywhere.

RONALD L. KORETZ, M.D.

Reply. From a theoretical point of view, Dr. Koretz is correct in his statement that when two treatments differ, this may be because one is really better or because the other is simply worse than no treatment at all. However, our working hypothesis relies on very concrete and worldwide accepted evidence: (1) Malnutrition (i.e., weight loss ≥10% of the body weight) is associated with a high risk of postoperative complications. (2) Of 41 RCTs on total parenteral nutrition (TPN) in surgical patients quoted by Koretz et al. (Gastroenterology 2001;121:970–1001), unfortunately only 3 (Br J Clin Pract 1988;63:53–58, Clin Nutr 1992;11:180–186, JPEN J Parenter Enteral Nutr 2000;24:7–14) involved exclusively malnourished cancer patients. As surgical oncologists, we would not willingly accept the results of studies that also included noncancer patients and, as nutritionists, we would feel uncomfortable with studies in which patients receiving nutritional support were not totally malnourished (with malnutrition being either marginal or only present in some patients). The 3 above-mentioned studies showed a statistically significant clinical benefit for perioperative TPN compared with control patients receiving standard intravenous therapy. These conclusions are also shared by Koretz because perioperative TPN decreases the absolute rate of complications by 18% in patients with upper gastrointestinal cancer. (3) Despite statements to the contrary, there are no data, except our study, on the effects of postoperative TPN in really malnourished cancer patients (Curr Opin Clin Nutr Metab Care 2001;4:451–456). (4) Both the American Societies for Parenteral & Enteral Nutrition and for Clinical Nutrition recommend that postoperative TPN should be started within 5 days if patients are unable to eat (JPEN J Parenter Enteral Nutr 1997;21:133–156).

As a result, we felt it was reasonable to compare enteral nutrition (EN) to a TPN regimen, which proved to be successful perioperatively in high-risk malnourished cancer patients (comment #2 above) and is recommended by various scientific societies (comment #4 above).

Our data did demonstrate an advantage for the EN regimen. With regard to the remaining issues raised by Dr. Koretz, we agree with his comments on the dose-response effect. Patients reported in previous studies by Braga and Gianotti were enrolled prior to the start of this multicenter trial, except those reported in Crit Care Med 2001;29:242–248; their accrual started after these authors completed randomization for their multicenter trial.

FEDERICO BOZZETTI, M.D.
MARCO BRAGA, M.D.
LUCA GIANOTTI, M.D.
LUIGI MARIANI, Ph.D.

SYMPATHETIC HYPERACTIVITY IN PRE-ASCITES


Sympathetic hyperactivity is a common finding in cirrhotic patients with ascites and is involved in the pathogenesis of ascites formation. However, sympathetic nervous activity in pre-ascitic cirrhosis is unknown. Therefore, the sympathetic nerve activity via the peroneal nerve to skeletal muscle (MSNA) and to skin was measured by microneurography in 12 patients with Child A, pre-ascitic cirrhosis, 16 Child C cirrhotic patients with tense ascites; 10 patients with mild congestive cardiac failure; and 10 normal control subjects. Mean MSNA in normal controls was 24 bursts/min, which was significantly less than that in both the Child A pre-ascitic (42 bursts/min; P < 0.01) and Child C cirrhotic patients with ascites (53 bursts/min; P < 0.01). Mean MSNA in the Child C cirrhotics, however, was similar to that in heart failure patients (60 bursts/min). Skin sympathetic nerve activity was normal in all groups. Mean plasma renin activity, serum aldosterone, and norepinephrine levels were all highly elevated.