Evolving questions of perioperative nutritional support

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Malnutrition remains a common problem in surgical patients. Its association with poorer outcomes has been demonstrated consistently over many years. The development of practical techniques of parenteral nutrition (PN) in the 1960s and early 1970s presented a unique opportunity to administer nutrients without relying on a functioning gastrointestinal tract. The hypothesis that malnutrition and its adverse effects could be corrected by nutritional support has been examined in numerous studies in the years since. Many employed PN. Although observational studies may be suggestive, it is now widely accepted that randomized clinical trials (RCTs) allow the strongest causal inferences to be drawn and provide the strongest evidence of the efficacy of interventions such as nutritional support. Ideally, variables other than the intervention being tested (i.e., nutritional support), which might influence the outcome of interest, are balanced among the groups being compared. These variables may be recognized or not, and random assignment to treatment groups is the best means to approach this balance. The outcomes of interest in many early studies were nutritional or metabolic variables, such as nitrogen balance. However, improvements in such endpoints with nutritional support often were not reflected in important clinical outcomes.[1] That the nutritional problems of surgical patients were not simply the result of a lack of substrate became clearer as the metabolic responses to surgical illness and their mediators were elucidated. Further, there was increasing recognition that PN was itself associated with complications. Consequently, outcomes with clinical significance, such as complication or death rates, have been the focus of many later studies.

The role of perioperative PN has become clearer in recent years with the completion of some large RCTs and with increasingly sophisticated approaches to review and synthesis of the relevant literature as a whole.[2,3] RCTs are challenging to conduct, and those addressing questions of nutritional support have often studied relatively small numbers of patients. Meta-analysis is one approach to the synthesis of available information from RCTs addressing a specific question. When appropriate, data from a number of studies can be aggregated to improve statistical power, for example to detect a significant treatment effect that might not have been apparent in small studies. Probably as important, meta-analysis also affords an opportunity to rigorously evaluate and compare individual trials and their results, and to identify uncertainties and directions for future research. This issue of the Journal contains an important paper by Heyland and associates (page 102), which describes a meta-analysis of randomized trials of perioperatively administered PN compared with standard care in surgical patients. The majority of patients had major elective gastrointestinal procedures. PN did not influence the death rate although it may have reduced complication rates, principally in malnourished patients. Meta-analyses and systematic reviews must be carefully planned and conducted if their conclusions are to be well founded, and, as readers, we need to be as careful in judging the quality of a meta-analysis as we are that of an individual trial. The important attributes of meta-analysis are well demonstrated in this paper. The authors describe a systematic approach to the relevant literature, examine *a priori* hypotheses using the techniques of meta-analysis and base their conclusions on objective, evaluable criteria. This approach allows us to judge the definitions and choices the authors have made and our confidence in their conclusions.

Even if we are not well acquainted with the subtleties of meta-analysis, Fig. 1 in Heyland's paper, illustrating the risk ratios and confidence intervals for each study, makes very clear the lack of any overall effect of perioperative PN on mortality. Why might these data fail to show such benefit for patients who face the stress and starvation of a major operation? Does this failure reflect flaws in the meta-analysis, problems with the individual studies or is there simply no major effect of the treatment (PN) in the population examined (primarily elective surgical

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patients)? The methods used to identify relevant work for the meta-analysis are clearly defined and are comprehensive. It seems unlikely that there are compelling data that have not been included. On the other hand, the authors may have been overinclusive. The nutrient prescriptions vary considerably among trials and some would not now be expected to be useful. For example, in the single largest study (678 of an aggregate of 2907 patients in the meta-analysis), calories were administered at a rate far below the rate of expenditure ("hypocaloric nutrition").[4] The PN group received intravenous protein in modest quantities for 5 days or more after surgery, whereas both PN and control groups received glucose in minimal quantities (150 g/d). Are there methodologic deficiencies in the studies identified? Certainly there are, as the authors highlight, but flawed studies may well be more likely to exaggerate treatment effects (i.e., a benefit from PN) rather than obscure them. Are the outcomes appropriate? Perhaps it is ambitious to expect that PN would be a deciding factor in the survival of patients with cancer and other serious conditions who undergo major surgical procedures. Heyland and associates conclude that major complication rates may be improved by PN, but definitions and reporting vary widely among individual trials. Was the PN optimal in terms of specific nutrients, adequacy of the substrate provided, and monitoring and complications? Probably it was not in many of the trials, at least by current standards. For example, hyperglycemia is accompanied by an increased incidence of wound infections and other complications but was not well managed in several studies.[5,6] The addition of glutamine to conventional PN solutions, as another example, has been associated with improved clinical outcomes in patients with acute illness in a number of clinical trials.[7,8] Is the net benefit of perioperative PN limited to a subset of patients, such as those who are malnourished? This is certainly consistent with current opinion and with the observation of a possible improvement in complications in malnourished patients in this analysis.[3]

Several current trends in nutritional support broaden the questions about perioperative support in surgical patients beyond that of whether to admit patients preoperatively for PN or to provide it postoperatively, or both.[9] With recognition of the adverse effects of PN and the varied functions of the gastrointestinal tract, the use of the enteral nutrition has increased rapidly. Its use will to continue to increase, both alone and in combination with parenteral feeding, as experience is gained. Our appreciation of the importance of micronutrients (vitamins and trace elements) and other nutrients with antioxidant properties is growing. Preoperative micronutrient supplementation in the elderly and other high-risk patients may prove beneficial in clinical trials that are ongoing. The preoperative period is also the optimal time to address macronutrient deficiencies, using oral supplements in mildly or moderately malnourished patients, enteral feeding when necessary in severely malnourished patients and brief periods of parenteral feeding when that is the only option. Of course in many circumstance, (e.g., ongoing infection or obstructing cancers) any nutritional gains made in delaying definitive surgery will be minor at best and outweighed by additional complications. Changes in postoperative care have also had an impact on the practice of nutritional support. The early resumption of oral intake and physical activity has reduced the adverse effects of starvation and immobility, which were routine occurrences in the past. Continuing improvements in pain management and other elements of perioperative care will further minimize stress responses to surgical illness and their metabolic consequences. Increased recognition that enteral feeding is often feasible postoperatively has also led to a decline in the use of PN. Lastly, the efficiency and effectiveness of nutritional support will likely be enhanced by the use of growth factors and by specific nutrients used for their pharmacologic effects.

Starvation is bad, so feeding must be good. Perhaps so in some circumstances, but the paper of Heyland and associates demonstrates that we need to know more about just which surgical patients will benefit and how best to nourish them. More generally, it encourages us to re-examine our assumptions about patient care when they have not been well tested, and it illustrates very well some of the tools available to do so.

References

1. Wilmore DW. Postoperative protein sparing therapy. *World J Surg* 1999;23:545-52.
2. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991;325(8):525-32.
3. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition [review]. *JPEN J Parenter Enteral Nutr* 1997;21(3):133-56.
4. Doglietto GB, Gallitelli L, Pacelli F, Bellantone R, Malerba M, Sgadari A, et al. Protein-sparing therapy after major abdominal surgery: lack of clinical effects. Protein-Sparing Therapy Study Group. *Ann Surg* 1996;223(4):357-62.
5. Pomposelli JJ, Baxter JK 3rd, Babineau TJ, Pomfret EA, Driscoll DF, Forse RA, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN J Parenter Enteral Nutr* 1998;22(2):77-81.
6. Schloerb PR, Henning JF. Patterns and problems of adult total parenteral nutrition use in US academic medical centers. *Arch Surg* 1998;133:7-12.
7. Ziegler TR, Young LS, Benfell K, Scheltinga M, Hortos K, Bye R, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. *Ann Intern Med* 1992;116:821-8.
8. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997;13:295-302.
9. Wilmore DW. Nutrition and metabolic support in the 21st century. *JPEN J Parenter Enteral Nutr* 2000;24(1):1-4.