Care Unit nurses for their diligence, help, and success in delivering enteral nutrition.

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Discussion

DR. MARTIN ALLGOWER (Pratteln, Switzerland): I think this beautiful demonstration has reminded us of the landmark pa-

per presented some years ago to this Association by John Border. He very rightly pointed out that there are three principles in dealing with major trauma, the first one being immediate total care of all lesions, particularly of the large bones. In this patient population there were no fractures. I do not know whether those patients had "prophylactic internal fixation" that their skeleton was spared. However, there are three important parts: immediate total care, judicious use of antibiotics, and most importantly, to give muscle fuel (branched chain amino acids) by enteral route, and to physiologically challenge the mucosa by this enteral administration.

My question is, what was the antibiotic tactic in your cases? Do you have one fixed policy?

I wanted to really remind you of this fundamental work of Border, which went exactly in the same direction as confirmed by this beautiful presentation.

DR. J. WESLEY ALEXANDER (Cincinnati, Ohio): Perhaps the first interest in immunonutrition began with a paper that was presented before this organization in 1980 by our group that showed simply increasing the amount of protein in the diet of seriously burned children resulted in improvement in survival as well as a number of immunologic functions.

During the next decade, both animal and clinical studies showed that early feeding compared with delayed feeding and feeding by the enteral route compared with to the intravenous route was of benefit. Perhaps the most important observations were that certain nutrients would have a beneficial effect because they altered the immune system. In general, these were arginine, glutamine, and the polyunsaturated fatty acids. Since that time, there have been six published prospective randomized controlled clinical trials, five of them double-blinded, which have shown a beneficial effect of immunonutrition.

The first of these was in burned children with a prototype formula that was done at the Shriners Burn Institute in Cincinnati. Four of the other studies were done with a formula which was derived from this prototype, namely Impact (Sandoz Nutrition, Minneapolis, MN), and the sixth one was done with Immune-Aid (McGaw, Inc., Irvine, CA), the product used in Dr. Kudsk's study. These formulas are basically similar.

It is important to recognize that the beneficial effects of these formulas are profound. These studies in the aggregate have shown that they will reduce hospital stay by approximately 20% and reduce wound complication and infection rates by 50% to 70%.

Dr. Kudsk's expertly executed study confirms and extends these previous investigations and adds new dimensions, in that there is a second control group which is quite interesting, without enteral access and who were basically nonfed. These patients had very similar results to the control group that received the isonitrogenous control diet with enteral access. In addition, he provides more evidence for the cost benefit of using immunonutrition in this group of patients.

I have basically three questions. First, were you surprised that the early-fed isonitrogenous and nonfed control groups had such similar results and can you explain why? Was this perhaps because the nonfed control group did not receive intravenous hyperalimentation?

Many of the outcome variables had borderline significance with p values between 0.05 and 0.1. How were the small numbers of patients in each group (16 *vs.* 17) selected for the study design, and why weren't more patients entered?

Finally, would you expect to show a benefit in the less seriously injured patient, and what would be your cut-off for injury severity at the present time?

DR. J. DAVID RICHARDSON (Louisville, Kentucky): I think this is an extremely important study because it offers tremendous potential benefit to injured patients and certainly these observations could conceivably be extended to other stressed patients as well. There are several other studies, as other discussants have alluded to, that have indicated that either a standard formula or an immune-enhancing formula may lower the risk of infectious complications.

Clearly, if one accepts these data and other similar studies at face value, I would submit that it would necessitate the placement of a feeding tube into the jejunum of virtually all seriously injured patients, as the authors seem to be recommending. I would further submit that the consequences of this action are tremendous in terms of cost of feeding, increased nursing care required, and potential complications from the placing of jejunostomies, particularly if there really are no defined benefits. I must admit that I am somewhat more skeptical than the other discussants about the defined benefits. I would think, therefore, that before we accept these out of hand, we should examine these data very closely.

First, I am confused by the control group, which certainly I would not in any way classify as a control group because patients were randomized only after a tube was placed. How were the control patients chosen? Ideally, it would seem to me that there should be randomization by intent to treat from the beginning. Your paper states that these patients were not randomized but were treated concurrently. I do not know what that means and do not really know how we can make anything of their inclusion into this paper. Certainly, the inclusion of 13 patients who have colon injuries, including 7 with major colon injuries, does potentially make a difference, whether it is statistically significant or not. In such a small group, the inclusion of 13 colon injuries in the control group when you only have 5 and 6 colon injuries, respectively, in the other two treatment groups potentially makes a difference.

Second, the authors infer in the manuscript and in their conclusion slide that the unfed patients did worse than fed patients when in fact, that is not the case. In every comparison between the standard formula and unfed patients, there was no statistically significant difference in outcome. So I think that needs to be clearly stated, and in that regard, this needs to be viewed as a negative paper. I think we ought to reject catch phrases such as "trends toward the higher complications" which the authors used because there was no difference between group II and group III.

Third, if there is no difference in standard enterally fed and unfed patients, I am curious as to how the authors would then rationalize those findings against previous papers from their own institution, which in fact have shown marked differences between patients fed standard low-bid enteral feedings and patients fed total parenteral nutrition.

Fourth, the incidence of abdominal abscesses seems very high in both the standard feeding and the control groups of 39% and 47%, respectively. Your own paper on colon injuries from

Memphis several years ago, if I remember, had approximately a 21% infection rate. In our gamma-interferon trial led by the Louisville group, which was actually a multicenter trial, the unfed group which had no gamma-interferon had an abscess rate of 24% in a similarly severely injured group of patients.

I always worry when things seem too good to be true, and a difference in abscess rate of six- and eightfold is striking in less than 20 patients and almost seems too good to be true. The question I would ask is, how do you logically explain these dramatic differences in such a very small series of patients?

DR. BRUCE M. WOLFE (Sacramento, California): I, as Dr. Richardson, was impressed that the major benefit was demonstrated with the special diet with a marginal outcome difference between the control fed and unfed patients. Are we therefore to conclude that the benefit of early enteral feeding is dependent in fact on provision of the special or immune-enhancing diet?

Second, in data presented in the manuscript, it is indicated that 88% of the fed patients experienced abdominal distention with approximately half requiring reduction in the rate of feeding. The delivery of nutrients directly into a small intestine that is affected by paralytic ileus leads to stasis of nutrients in the lumen of the gut and bacterial digestion of the nutrients. Carbon dioxide and hydrogen are liberated and a very rapid and impressive abdominal distention may occur. Are there any measures of the severity of this phenomenon, such as worsening of abdominal compartment syndrome, prolongation of the need for mechanical ventilation, or other measure of this problem? Many of us find it difficult to continue enteral feeding in the presence of worsening abdominal distention.

Finally, are there any prospects for sorting out which and how much of these special nutrients are in fact needed to achieve these effects? For example, do we really need to deliver 18 calories per kilo during the first 8 to 10 days after injury in subjects who do not uniformly have malnutrition? Perhaps the gastrointestinal side effects could be minimized by delivering a lesser amount of feeding.

DR. PAUL R. SCHLOERB (Kansas City, Kansas): This product combines the alleged values of the individual nutrients such as arginine, glutamine, and nucleotides, as was listed on your slide.

I would like to request that you prioritize these various nutrients. The company has put them together in this product, has loaded the shotgun, so to speak, and you have fired it pretty effectively. A nice paper.

DR. DONALD E. FRY (Albuquerque, New Mexico): This has been for me the most provocative manuscript that has been presented at this organization this year. I would suggest that the data are really going to need to be examined in some detail and validated by other investigators before we close the antibiotic pharmacies back at our hospitals.

I guess the question here is, are we studying nutrition or are we studying abscess? Abscess results in more antibiotic usage, more hospital days, more hospital costs. And actually all of the data here could be rearranged and have abscesses be the independent variable rather than the nutritional regimen that the patients received.

Because the Memphis group has been the bastion of primary closure of colonic injuries, I could not help but notice that the group that had the lowest abscesses seemed to have the worst colon injuries. The question now comes, how were the colon injuries managed? Were there differences in who received colostomies versus who had primary repair?

I would really like to pose to Dr. Kudsk if he could identify those four class 5 patients in the immunotreated group and tell us whether they had a higher rate of colostomy formation and hence had lower abscess rates because of perhaps fewer complications.

I would again reiterate Dr. Richardson's comments that group 2 and group 3 patients have a greater than twofold rate of abscess formation than the Memphis group has previously published in their own series, and I guess we still are confronted with the issue here, are the groups comparable? Is abscess really the variable and not the nutritional support regimen?

Finally, I think it is important to bear in mind when we talk about enhancing the gut barrier, that for the colon the short-chain fatty acids become more important than such things as glutamine. I am curious if the authors could share with us the differences in the fermentable fiber content that may have existed in the various preparations and whether that, too, is another important consideration in the nutritional support strategies for these patients.

DR. KENNETH A. KUDSK (Closing Discussion): I have been involved with this topic for approximately 15 years, and, as a result, have a large patient population in which to carry out these randomized prospective studies. I did not believe this product was going to work before the study. I tried to keep everything blinded as much as possible and these are the results.

Dr. Allgower, I appreciate you calling attention to Dr. Border's article regarding the antibiotics and specifically, the need to provide protein. Our antibiotic tactics are as follows. If patients have a penetrating wound to the abdomen with hollow organ injury, 24 hours of antibodies are administered and then discontinued. If there are orthopedic procedures or plastic surgery procedures such that our colleagues desire prophylactic antibiotics for 4 or 5 days, then we allow that, but generally, for any intra-abdominal injuries, 24 hours of antibiotics and no more. There were femur fractures in some blunt trauma patients, and they were fixed immediately. Most of the injuries, however, were penetrating trauma.

Dr. Alexander pointed out the lack of significant differences, if you will, between the isonitrogenous diet and the nonfed control. Part of the point I tried to bring out was that although the Abdominal Trauma Index (ATI) and the Injury Severity Score (ISS) were similar, the amount of blood loss and probably severity of injury appeared to be less in the unfed control. Yet consistently in everything we measured, the unfed control group had the highest rate of intra-abdominal abscess, the highest rate of pneumonia, the highest rate of major infectious complications, the most days on the ventilator, and the most days in the hospital. I do not think that this can be ignored.

We did a statistical analysis. We would have needed 40 patients in both the isonitrogenous control and in the unfed control groups to reach statistical significance. This is about the same number the Moore brothers required in their first study, to show a difference between unfed controls and patients fed enterally.

How did we select such a small number? Although we projected this number from our enteral/parenteral study, an interim analysis was done after completing 20 patients which confirmed that we needed approximately 30 total, 15 in each group. By the 30th patient, we also had the 31st, 32nd, and 33rd patient enrolled. After those were complete, we then locked the database and we did have statistical significance.

Dr. Alexander also asked about the less severely injured—who should we use this immune-enhancing diet in? Basically, I think we have a very select patient population here—high injury severity, high ISS—which as we previously showed, respond to route of administration, and now we show response to type of nutrition as well. This is approximately 1.6% of the patient population admitted to our hospital out of 4300 trauma patients.

We basically give this immune-enhancing diet to anyone we think is at significant risk of developing septic complications after their injury. We maintain it for 4 to 5 days until it is clear that they are either getting better and are not going to get a septic complication; if they are getting worse, we continue it.

Dr. Richardson was a little critical of the control group that we followed prospectively. They certainly were not randomized. We did not feel we could ethically do that because Dr. Moore's study had previously shown that you get worse results when you do not feed these patients. These were just people who had not been cannulated, probably because of the fact that, although they had colon injuries and small bowel injuries, they did not have very much blood loss. It was a decision of the clinician that this patient was probably not going to have a very difficult course.

There is a little difference between these patients and those in our previous study of enteral feeding *versus* total parenteral nutrition (TPN). But it is unclear to me whether the patients who are moderately injured, are having some deleterious effects with TPN. My own feeling and data from the laboratory suggests that TPN has a negative impact on mucosal immunity, but I believe there also is a difference between an unfed population and patients who are getting intravenous nutrition.

You raised the question also about the incidence of intra-abdominal abscess being particularly high. Dr. Croce reviewed our experience with 800 patients comparing intra-abdominal abscess rate against the abdominal trauma index. The incidence of abdominal abscess in someone who has an ATI of approximately 30 is 32%. Our average ATI in this study was 31, and we had an overall intra-abdominal abscess rate of 30%. That other study was not stratified by route or type of nutrition. The present study shows that most of those increased abscesses occur in patients who are not fed rather than people who are fed via the gastrointestinal tract.

Distention! I am more surprised that 50% tolerated the feedings without needing to turn down the rate. I am not surprised in this severely injured population patient that we had to turn the rate down. Abdominal distention does not always mean bowel distention in these injured patients. We had no problems with abdominal compartment syndrome.

In answer to Dr. Schloerb's question, I know a powder form is more inconvenient, but it does not clog the tubes. I do not know whether it is the glutamine or arginine or what that makes the difference. I doubt that anyone will fund a study that would take such a large population of patients to identify the effectiveness of each component.

Finally, looking at our colon injuries, Dr. Fry, one of the four on the immune-enhancing diet group had a primary anastomosis, two of the four in the unfed group had an anastomosis. Only one of the unfed patients developed an intra-abdominal abscess. There was no fiber in any of these products, so I doubt that fatty acids played a role.