

GUT FAILURE—PREDICTOR OF OR CONTRIBUTOR TO MORTALITY IN MECHANICALLY VENTILATED BLUNT TRAUMA PATIENTS?

C. Michael Dunham, MD, David Frankenfield, MS, Howard Belzberg, MD, Charles Wiles, MD, Brad Cushing, MD, and Zina Grant, MSA

Thirty-seven ventilator-dependent blunt trauma patients (ISS 36 ± 15) were randomized at 24 hours after injury to receive parenteral (TPN) ($n = 15$), enteral (TEN) ($n = 12$), or parenteral plus enteral (PN/EN) ($n = 10$) nutrition. The TEN and PN/EN patients had endoscopically placed transpyloric feeding tubes. Patients who had nutritional complications were two TPN (13%), three TEN (25%), and five PN/EN (50%). Enteral complications were tube occlusion (two), failed duodenal intubation (one), patient extubation of feeding tube (one), gastric reflux (two), and abdominal distention (two). Mortality rates were not different between the groups, but were significantly related to the nutrition-associated complications ($p = 0.01$): four deaths in ten (40%) with complications and one death in 27 (3.7%) without complications. All four deaths associated with complications occurred in the four with gastric reflux or abdominal distention. No deaths occurred in the other 18 TEN or PN/EN patients ($p = 0.0001$). Of the four deaths, three were associated with ARDS and respiratory infection (75%). **Conclusions:** In mechanically ventilated blunt trauma patients, endoscopic transpyloric tube placement and feeding has a substantial failure rate (36%). Intolerance to duodenal feeding has a remarkably high mortality (100%) in patients in whom gut dysfunction may be a manifestation of injury severity or directly affect survival.

THE ROLE of gastrointestinal tract function in critical illness remains a focus of intense investigation.¹⁻⁶ The gut may play a central role in the adverse sequelae that can accompany serious clinical pathologic states.^{6,7} Investigators have hypothesized that enteric feedings may mitigate transmigration of gut bacteria or their products by preserving the gut mucosa.⁸ Additionally, enteric feedings may need to be initiated early to optimize efficacy.^{4,9}

The use of enteric feedings in trauma patients is problematic since gastrointestinal intolerance to feedings may occur.¹⁰⁻¹² Furthermore, the use of esophagogastrroduodenal tubes is associated with a variable occurrence of complications.^{11,13-16} To assess the potential benefits and complications of early enteric nutritional infusion in seriously injured and ventilator-dependent blunt trauma patients, a prospective, randomized study was performed at the Maryland Institute for Emergency Medical Services Systems' Baltimore Shock Trauma Center.

MATERIALS AND METHODS

Patients were randomized into one of three study arms, which varied by the route of nutrient administration. One arm consisted of patients who received all calories and protein parenterally (TPN), a second group had all calories and protein administered enterally (TEN), and a third group had approximately half of their total calories and protein administered by the parenteral route and the other half by the enteral route (PN/EN). The TPN subset—the control group—received the standard protocol for critically injured, blunt trauma patients used at this institution.

Patients were evaluated approximately 18 hours after admission for possible study inclusion and randomization. Patients randomized had the following: (a) blunt traumatic event, (b) Glasgow Coma Scale (GCS) score ≥ 5 , (c) Injury Severity Score (ISS) ≥ 15 , (d) no spinal neuropathy above the eighth thoracic spinal level, (e) no major fluid restriction requirement, (f) ages 18 to 60 years, (g) were able to undergo upper gastrointestinal endoscopy, and (h) respiratory insufficiency that mandated the need for a mechanical ventilator for at least 48 additional hours for one or more of the following conditions: severe brain injury, $\text{PaO}_2/\text{FIO}_2 \leq 250$, compliance ≤ 35 mL/cm, maximal inspiratory force < -30 cm, vital capacity < 15 mL/kg. Patients were not considered if randomization did not take place within 30 hours after admission or admission did not occur within 12 hours after injury.

The total projected nonprotein calories administered was $1.3 \times$ basal energy expenditure (BEE) as determined by the Harris-Benedict equation. Nonprotein calories (NPC) were given in the form of lipids (30%) and carbohydrates (70%).

From the Maryland Institute for Emergency Medical Services System, Baltimore Shock Trauma Center.

Reprint requests: Charles Wiles, MD, Shock Trauma Center, 22 S. Greene St., Baltimore, MD 21201.

The ratio of NPC to nitrogen was 105:1, which provided a protein load of approximately 1.75 g/kg/day. For patients with a body weight $\leq 120\%$ of ideal, actual body weight was used for all calculations. When body weight was $>120\%$ of ideal, metabolically active weight was calculated as ideal weight plus 0.25 times the difference between actual and ideal weight.

All patients received a caloric-protein infusion rate that delivered half of the projected calories and protein by 24 hours after randomization and the full infusion rate by 48 hours after randomization. Patients randomized to either of the enteric arms had a transpyloric tube placed by endoscopic techniques. All patients in the study had a translaryngeal and esophagogastric decompression tube.

Parenteral infusate constituents included a standard dextrose-lipid-amino acid (AA) mixture without branched-chain amino acid (BCAA) enrichment. The TPN admixture was 6.7% AA (19% of which was BCAA) and 23.1% dextrose, which equals 67 g protein (10.7 g N) and 231 g dextrose (785 kcal/L). A soybean oil-based lipid emulsion (340 kcal/L of AA-dextrose) was administered separately over 24 hours and provided 30% of NPC. The 1125 NPC per liter of AA-dextrose-lipid provided a total NPC:N ratio of 105:1. Standard multivitamin and multitrace elements were added daily.

The enteric infusate consisted of one can of Traumacal (Mead Johnson) (casein protein source, soy and MCT oil, corn syrup, and sugar) combined with two containers of Liquid Carbohydrate (Naveco) (hydrolyzed corn starch) and three scoops of protein powder (whey). This combination yielded 480 NPC (30% lipid), 29 g protein, a NPC:N ratio of 103:1, and 1.5 NPC/mL, in a total of 320 mL. Multivitamin elixir (Theragran, 5 mL/d) was added to supply 100% of the recommended daily allowances for vitamins. Magnesium and phosphorus levels were monitored and supplementation was provided as needed. Traumacal was used as the base enteral feeding since it is the standard at our institution. Blue food coloring was routinely added to the enteric infusate.

The nutritional regimen outlined in the protocol continued for 7 days after randomization. Whenever patients received less than 75% of the projected calorie-protein infusion during any 24-hour period, they were considered to have a nutrition-related complication. These were further categorized as enteral-related or parenteral-related problems. Patients were assessed for severity of injury by admission stratification data indices at the time of entry into the study. The stratification data were collected in a prospective manner with verification by the admitting trauma surgical attending physician and his staff. The entry of these data into the clinical trauma registry is routine for all patients admitted to this trauma center.¹⁷

Specific events occurring in the first week were recorded as early outcome variables of interest. These items included (a) randomization arm, (b) weight, (c) height, (d) protein-calorie projections and amounts received, (e) upper gastrointestinal complications, and (f) venous catheter complications. Gastric reflux of duodenal feedings was determined by the presence of blue food coloring in the gastric tube effluent and the radiographic demonstration that the tip of the feeding tube lay in the transpyloric position. On study days 1, 3, and 7 (hospital days 2, 4, and 8) the following metabolic and physiologic measurements were made: serum glucose, bilirubin, albumin, cholesterol, C-reactive protein, and transferrin, and blood urea nitrogen.

Data related to the entire hospitalization were utilized as additional measures of outcome: ventilator days, ICU days, total hospital stay, presence of adult respiratory distress syndrome (ARDS), respiratory infection, any infection, renal failure, icterus (serum bilirubin >5 mg/dL), death, and hos-

pital and professional charges. All infections were defined by predetermined criteria¹⁷ and the adult respiratory distress syndrome was defined by the concomitant presence of the following for ≥ 3 days: (a) pulmonary artery hypertension, (b) $\text{PaO}_2/\text{FIO}_2 < 200$, (c) bilateral interstitial infiltrates evident on chest films, and (d) a static pulmonary compliance ≤ 30 mL/cm. Virtually all these data were also available from the trauma registry. The hospital charges were obtained from the institute and professional charges from physician professional corporation finance officer. All data from the trauma registry and the finance officers were blinded, since these sources had no knowledge of the patient's status relative to the research arm assigned.

The data are displayed as the mean and standard deviation. A procedure that fits least-squares estimates to linear regression models was used to determine correlations between continuous variables. A method of least squares to fit general linear models was used to assess relationships between continuous and categorical data. The Fisher's exact test was used to compare categorical data. When performing multiple group comparisons, Fisher's exact test was used for categorical data and ANOVA was performed for analysis of continuous data.

This study was approved by the University of Maryland at Baltimore Institutional Review Board for Human Investigations.

RESULTS

One patient died on the fourth study day without any apparent complications associated with TPN. Since this patient did not survive the 7 study days to establish presence or absence of nutrition related complications, he was excluded from subsequent analysis. The other 37 patients were randomized as follows: TPN, 15; TEN, 12; and PN/EN, 10 and no differences in injury severity were found among these groups (Table 1). The distribution of celiotomies during the first 24 hours was similar in the initial three study arms (TPN 60%, TEN 42%, and PN/EN 40%), for an overall incidence of 49%.

In the TPN arm, eight patients successfully completed the 7 days of nutrient infusion. Five patients were ready to eat within 7 days and two patients developed nutrition-related complications—both management errors that caused the infusion rate to be set inadequately. The TEN arm contained six who completed the nutritional regimen. Three others were ready to eat within the first week and another three patients had enteral-related complications: one occlusion of the transpyloric tube, one ileus, and one unin-

Table 1
Admission stratification data

	TPN	TEN	PN/EN	<i>p</i> Value
Number of patients	15	12	10	
GCS score	12 \pm 3	11 \pm 5	11 \pm 4	0.51
ISS	38 \pm 12	34 \pm 18	37 \pm 15	0.78
Lactate level (mmol/L)	4.7 \pm 2.0	3.7 \pm 1.7	4.1 \pm 1.7	0.34
Blood requirement (L)	2.1 \pm 1.8	2.2 \pm 1.5	2.9 \pm 3.4	0.64

tentional extraction of the tube without replacement. The PN/EN arm had three who received the 7-day nutritional infusion. Two other patients were ready to eat within 7 days and another five patients had nutrition-related complications, all related to the enteric infusion. These problems were gastric reflux in two patients, transpyloric tube occlusion in another patient, failure to intubate the duodenum in one, and small bowel ileus on study day 3 with subsequent death on study day 7 in the fifth patient. There were no technical or septic central venous catheter complications during the 7 study days in the TPN or PN/EN patients. The nutrition-related complication rate for the 37 patients was 27.0%. These complications were more frequent in the enteric groups compared with the TPN arm (Table 2).

The overall mortality rate was 13.5% and the occurrence for the three groups is shown in Table 3. The death rate in the PN/EN group was substantially greater than in the TPN (odds ratio = 6.0) and TEN (odds ratio = 4.8) groups; however, no intergroup mortality combination reached statistical significance. An analysis of all 37 patients revealed that deaths were related to the development of nutrition-related complications ($p = 0.01$; odds ratio = 17.3), but not to ISS, amount of blood infused, admission lactate levels, or the need for celiotomy. There was only one death in the 27 patients (3.7%) without nutrition-associated complications compared with four deaths in ten (40%) with such complications (Table 4).

There were 22 patients randomized to receive enteric nutritional support, i.e., a proximal gut challenge

Table 2
Nutrition-related complications

	Number of Patients	Complications	Percentage
TPN	15	2	13
TEN	12	3	25
PN/EN	10	5	50
TEN and PN/EN	22	8	36
		Odds Ratios	
TEN compared with TPN		2.2	
PN/EN compared with TPN		6.5	
PN/EN compared with TEN		3.0	
TEN and PN/EN compared with TPN		3.7	

Table 3
Mortality rates

	Number of Patients	Number Who Died	Percentage
TPN	15	1	6.6
TEN	12	1	8.3
PN/EN	10	3	30.0
TEN and PN/EN	22	4	18.2
TPN and PN/EN	25	4	16.0
TPN and TEN	27	2	7.4

Table 4
Relationship of nutrition-related complications to mortality

	Patients	Number Who Died
No complications		
TPN	13	1
TEN	9	0
PN/EN	5	0
Totals	27	1 (3.7%)
Complications		
TPN	2	0
TEN	3	1
PN/EN	5	3
Totals	10	4(40.0%)

(TEN and PN/EN groups). All four deaths in patients randomized to undergo enteral feedings occurred in the eight patients with enteral-related complications (three TEN and five PN/EN), for a 50% mortality rate. More specifically, the reason for study withdrawal in all four of the patients who died was clinically evident impairment in small bowel peristalsis (ileus with abdominal distention in two and gastric reflux of duodenal feedings in two). None of the other four with enteric complications (those without clinically obvious peristaltic dysfunction) died. There was a significant difference in mortality between those with gut dysfunction (4 of 4 or 100%) and those without gut dysfunction. This is true no matter whether the group without gut dysfunction includes the four with other enteric-related complications ($n = 18$; $p = 0.0001$) or excludes them ($n = 14$; $p = 0.0003$).

Characteristics of the four enteric-fed patients who died are shown in Table 5. Age was 43.2 ± 7 years and mean ISS 31.3 ± 19 . Three patients developed ARDS and respiratory infection (75%) compared with four with ARDS (22%) ($p = 0.08$; odds ratio = 10.5) and seven with respiratory infection (39%) ($p = 0.22$; odds ratio = 4.7) in the other 18 patients randomized to TEN or PN/EN. The one patient who died in the TPN arm was 20 years old, had an ISS of 38, completed the 7 days of nutritional support, developed respiratory infection and ARDS, and succumbed on the 18th hospital day. Other than mortality and enteric-related complications, there were infrequent differences among the three groups relative to metabolic and physiologic outcomes (first week) and measures of hospital severity, e.g., hospital days, professional and hospital

Table 5
Characteristics of the four enteric-fed patients with peristaltic gut dysfunction who died

Patient No.	Study Arm	Age (years)	ISS	ARDS	Respiratory Infection Present	LOS (days)
1	TEN	45	15	Yes	Yes	31
2	PN/EN	34	34	Yes	No	8
3	PN/EN	51	19	Yes	Yes	56
4	PN/EN	43	57	No	Yes	30

Table 6
Nutritional intake for patients receiving all 7 days of the nutrient regimen

	TPN (n = 8)		TEN (n = 6)		PN/EN (n = 3)	
	Protein	Calories	Protein	Calories	Protein	Calories
Goal	134 ± 11	2280 ± 165	129 ± 20	2153 ± 287	136 ± 6	2240 ± 192
Day 1	49 ± 29	906 ± 462	67 ± 27	1065 ± 435	71 ± 47	1154 ± 904
Day 2	108 ± 18	1886 ± 438	89 ± 50	1427 ± 809	106 ± 36	1838 ± 857
Day 3	128 ± 14	2159 ± 447	122 ± 35	1963 ± 551	138 ± 13	2120 ± 184
Day 4	134 ± 11	2352 ± 351	133 ± 22	2148 ± 325	130 ± 10	2200 ± 184
Day 5	133 ± 13	2153 ± 396	119 ± 42	1910 ± 669	167 ± 66	2543 ± 779
Day 6	127 ± 20	2167 ± 418	129 ± 29	2083 ± 435	138 ± 18	2137 ± 59
Day 7	133 ± 11	2110 ± 341	120 ± 22	1931 ± 353	132 ± 23	2218 ± 335

Days 1-7 are hospital days 2-8.

charges, etc. For the 17 patients completing all 7 days of nutritional support, there were no significant differences in the amounts of nitrogen or calories projected or given (Table 6).

DISCUSSION

Outcome following mechanical trauma may be related to injury severity, preinjury host state, therapeutic interventions, and the development of infections or organ failure. Administration of substrate into the intestinal lumen may be necessary to attenuate host adverse conditions following a septic or traumatic insult,^{2,3,5,6,18} and efficacy may be realized only with early administration.^{4,9} However, other investigators have found that trauma patients may have an impairment in gastric emptying^{11,19} or small bowel function.¹² Furthermore, the resultant inability to provide adequate caloric and protein administration may be associated with a worse outcome.¹⁹

The aim of this study was to evaluate the potential benefits of intestinal feedings in seriously injured patients with blunt trauma who survived the first 48 hours following injury. The study rationale to utilize endoscopically placed transpyloric tubes in the enteric groups was based on the fact that a significant number of blunt trauma patients do not require celiotomy²⁰ and often have impaired gastric emptying.^{10,21} In fact, 50% of the patients in this study did not require celiotomy. Another reason for selecting this method of tube placement is that in ventilated trauma patients frequently it is difficult or impossible to pass an intragastric tube through the pylorus.²¹

In the current study, the patients had incurred moderate to severe injury based on ISS, GCS score, admission lactate levels, and blood requirements, and the need for mechanical ventilation²² and celiotomy.²⁰ There were no significant differences among the patients randomized to the TPN, TEN, and EN/PN groups relative to these factors.

The nutritional-related complication rate in patients undergoing enteric feeding was clinically significant (36%) and substantially greater than in those receiving

TPN (Table 2). The two complications in the TPN group were potentially avoidable, since they were related to failure to follow the precise protocol infusion rates, which were at customary clinical levels. However, the rates of complication in the enteric arms were noteworthy and the problems were not readily preventable. The eight complications in the enteric-fed group represented a failure of the transpyloric methodology used: failure to intubate the duodenum, tube occlusion, impaired gut peristalsis, and patient extubation. The obvious immediate clinical problem with nutrition-related complications is that caloric and nitrogenous requirements of the critically injured may not be met.

The mortality rates were not significantly different among the three principal groups or by any other rearrangement. However, when the patients in the three arms were combined for analysis, a significant relationship was found between mortality and nutrition-related complications (Table 4). None of the other factors likely to affect outcome such as ISS, blood requirements, admission lactate levels, or the need for a celiotomy in the first 24 hours was significant.

It is clear that the most constant nutrition-related complication in the four enteric-fed patients who died was the presence of clinically apparent peristaltic dysfunction. All four of these patients with enteric-associated deaths were withdrawn from the study directly because of impairment in small bowel peristalsis (ileus with abdominal distention or gastric reflux of duodenal feedings). The small bowel has been shown to function even when gastric and colonic peristalsis is impaired, such as in patients with surgical²³ or abdominal¹ trauma or brain injury.²⁴ However, other investigators have described small bowel intolerance in a significant subset of trauma patients¹² and a differential response of the gut in the critically ill,²⁵ suggesting that there may be patients who have had such a systemic insult that the entire organ becomes affected. McDonald et al. demonstrated a close relationship between gut dysfunction and burn wound size, with an attendant increase in mortality.²⁶

None of the 14 enteric-fed patients without compli-

cations, nor any of the four who failed enteric feeding without clinically apparent gut dysfunction (tube occlusion, failure to intubate the duodenum, or self-extubation) died. Although there may be potential benefits in instituting early gut feedings in critically ill patients,^{2,5} the advantage may be negated by the difficulties associated with esophagogastroduodenal tubes, especially in patients with proximal gut impairment.

Factors contributing to the mortality associated with peristaltic dysfunction may have been the presence of a larger number pharyngeal tubes in the enterically fed group. Each patient in the enteric groups had a trans-laryngeal, pharyngoesophagogastric, and pharyngoesophagogastroduodenal tube compared with two pharyngeal tubes in the TPN group. Elpern et al. found a 77% incidence of aspiration in patients with both pharyngoesophageal and tracheal tubes.¹³ As well, the enteric groups underwent upper gastrointestinal (UGI) endoscopy, but the TPN group did not. A number of complications with esophagogastroduodenal tubes have been described: aspiration pneumonia,^{13,16} unintentional tube removal,^{11,16} difficulty in tube placement,^{15,16} and tube occlusion.^{14,16} It seems clear that UGI endoscopy and triple pharyngeal intubation alone did not substantially increase the mortality rate, since 18 such patients survived. However, overt proximal gut dysfunction was present in all four patients who died with nutrition-related enteric complications, and three of the four developed pulmonary infections and ARDS.

This study suggests that, when the gut works, seriously injured (ventilator-dependent) patients with blunt trauma tend to do well. However, there is a high incidence of failure to provide adequate calories and nitrogen using an endoscopic-placed transpyloric method for intestinal feeding in those patients. Furthermore, the patients with intolerance to nutrient administration via the esophagogastroduodenal route have a substantial mortality rate. The gut failure and high death rate may be related to the fact that intestinal organ dysfunction is an expression of a more severe state of criticality and a guarded outcome. Furthermore, utilization of the gut when it is dysfunctional may increase iatrogenic complications and contribute to a dismal outcome. The present study in ventilator-dependent blunt trauma patients failed to demonstrate a survival benefit of duodenal feedings.

Although there is other evidence that enteric feedings may be beneficial, clinicians instituting such support in ventilator-dependent blunt trauma patients should monitor gastrointestinal tolerance very carefully. Feedings should not be instilled into the duodenum when there is proximal small bowel peristaltic dysfunction. Finally, one must consider that using a pharyngo-transpyloric-duodenal catheter may be deleterious in ventilated patients with blunt trauma who demonstrate intolerance to duodenal feedings.

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