Original Communication

Tolerability and Safety of Enteral Nutrition in Critically Ill Patients Receiving Intravenous Vasopressor Therapy

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Abstract

Background: Enteral nutrition (EN) is recommended within the first 24–48 hours following admission to an intensive care unit (ICU) once resuscitation and hemodynamic stability have been achieved; however, hemodynamic stability is not well defined. *Objective*: To evaluate the tolerability and safety of EN in critically ill patients receiving intravenous (IV) vasopressor therapy. *Methods*: A retrospective medical record review was conducted in an urban academic medical center and included adult ICU patients from 2011 who received concomitant EN and IV vasopressor therapy for ≥1 hour. EN tolerance was defined as an absence of gastric residuals ≥300 mL, emesis, positive finding on abdominal imaging, and evidence of bowel ischemia/perforation. *Results*: Two hundred fifty-nine patients received 346 episodes of concomitant EN and IV vasopressor therapy. Overall EN tolerability was 74.9%. Adverse events included rising serum lactate (30.6%), elevated gastric residuals (14.5%), emesis (9.0%), positive finding on kidney/ureter/bladder radiograph (4.3%), and bowel ischemia/perforation (0.9%). An inverse relationship was found between maximum norepinephrine equivalent dose and EN tolerability (12.5 mcg/min for patients who tolerated EN vs 19.4 mcg/min, $P = .0009$). This relationship remained statistically significant after controlling for other variables ($P = .019$). Patients who tolerated EN were less likely to have received dopamine (63.8% vs 77.6%, $P = .018$) or vasopressin (58.9% vs 77.9%, $P = .0027$). These patients received concomitant therapy for less time and received more nutrition. *Conclusions*: Most patients receiving IV vasopressor therapy tolerate EN. Tolerability was related to the maximum cumulative vasopressor dose and may be related to the specific vasopressor administered. (*JPEN J Parenter Enteral Nutr*. 2013;37:641-651)

Keywords

adult; critical illness; enteral nutrition; vasoconstrictor agents

Clinical Relevancy Statement

Data supporting provision of enteral nutrition (EN) to patients requiring intravenous (IV) vasopressor therapy for hemodynamic support are limited. This retrospective study suggests that EN is safe and well tolerated in patients receiving IV vasopressor support equivalent to 12.5 mcg/min of norepinephrine or less.

Introduction

In 2009, the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) collaborated and released guidelines for the provision of nutrition therapy in adult critically ill patients.[1] The European Society of Parenteral and Enteral Nutrition has also written guidelines for the management of enteral nutrition (EN) therapy in hospitalized intensive care unit (ICU) patients.[2] For the majority of patients, EN is preferred over parenteral nutrition (PN) because of its promotion of the functional and structural integrity of the gut and its reduced rate of infectious complications.[3,4] Moreover, EN is recommended within the first 24–48 hours following admission to an ICU once resuscitation and hemodynamic stability have been achieved. Although it is recommended that EN be withheld in patients requiring significant hemodynamic support, including high-dose catecholamine agents,[1] the definition of "high-dose" catecholamine agents has not been not made in this setting.

There is considerable controversy regarding the use of EN in patients requiring intravenous (IV) vasopressor support. Administration of catecholamine therapy has been associated with reduced EN tolerance.[5] Splanchnic perfusion is reduced in sepsis and shock, yet vasoactive agents have demonstrated both improved and diminished perfusion.[6-9] Inadequate perfusion increases the risk of experiencing rare but serious adverse events such as mesenteric ischemia and bowel perforation. Data examining the safety and tolerability of EN in patients requiring IV vasopressor support are limited.[10] Berger et al[11] demonstrated that EN was well tolerated in 23 cardiac surgery patients requiring IV vasopressor support. In a smaller study by Revelly et al,[12] an increase in splanchnic blood flow was observed when cardiac surgery patients requiring IV

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vasopressor and ionotropic support were given EN. No signs of splanchnic ischemia were observed in this study. Outcome data supporting EN in patients requiring IV vasopressor support are limited to a single study but suggest that early EN in this population may confer a survival advantage over provision of late EN.[13]

Methods

The study was conducted in an urban academic medical center (779 licensed beds, 126 ICU beds). Although no institutional guideline exists regarding provision of EN to the critically ill patient at our hospital, general practice is guided in a multidisciplinary approach in accordance with current guideline recommendations. Our multidisciplinary team includes registered dietitians who are Certified Nutrition Support Clinicians and provide patient-specific recommendations for timing of EN initiation, product choice, and goal caloric needs.

To identify patients eligible for inclusion, we performed an electronic medical record search for a 1-year period (2011). Patients had to be concomitantly receiving "tube-feeding volume" and an IV vasopressor (dopamine, epinephrine, norepinephrine, phenylephrine, and/or vasopressin). EN and IV vasopressor overlap was defined as (1) a charted event of an IV vasopressor infusion occurring between the start and end of the tube-feeding volume being charted or (2) a charted event of the tube-feeding volume occurring between the start and end of a charted IV vasopressor infusion. Patients could be included more than once in the study if more than 1 episode of concomitant EN and IV vasopressor therapy occurred during the hospital admission. If an interruption of either EN or IV vasopressor therapy (resulting in loss of concomitant administration) occurred for ≥24 hours, any subsequent resumption of concomitant administration was counted as a second episode for that patient. Patients were excluded if they were ≤18 years old and were treated in a nonadult ICU (pediatric or neonatal), if the overlap of EN and IV vasopressor was ≤1 hour, or if data were identified as missing or incomplete during chart review.

Demographic data, medical service at the time of EN/IV vasopressor overlap, duration of overlap, and type of shock were recorded. EN data collected included caloric density of the EN product, goal rate, initial and mean rate during overlap, and whether gastric residuals ≥300 mL occurred. Percent goal nutrition achieved during overlap and mean daily caloric intake were calculated as follows: mean EN rate during overlap ÷ goal EN rate and (mean EN rate during overlap × 24 × caloric density of EN) ÷ patient weight, respectively. Vasopressor data collected included agents used and the initial, mean, and maximum dosages during overlap episode. Vasopressor dosages were converted to norepinephrine equivalents using the following formula: norepinephrine equivalents = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷ 10] + [vasopressin (units/h) × 8.33].[14,15] Additional data collected included concomitant inotropes (dobutamine, isoproterenol, milrinone), select promotility agents (erythromycin, metoclopramide, methylnaltrexone, oral naloxone), paralytic infusion (cisatracurium or vecuronium), pentobarbital, and mean fentanyl equivalent dose (where 10 mg IV morphine and 1.3 mg IV hydromorphone were considered to be equivalent to 100 mcg IV fentanyl).[16,17] Stool and emesis output were recorded for all patients. For overlap episodes <24 hours in duration, stool and emesis output were recorded for 24 hours after the overlap episode occurred. If EN was stopped before IV vasopressor therapy, the reason for cessation was noted. Additional safety data collected included serum lactate measurements during overlap, diagnostic imaging including kidney/ureter/bladder radiograph (KUB) and abdominal computed tomography (CT) results, and bowel ischemia/perforation events. Mortality and primary cause of death were noted.

Outcomes

The primary outcome of this study was EN tolerance. Consistent with previous studies,[5,18,19] a composite definition of tolerance was used and required absence of all of the following: gastric residuals ≥300 mL, emesis, a positive finding on KUB or abdominal CT, and bowel ischemia/perforation. Secondary outcomes included rates of adverse events, characterization of IV vasopressor dosages during overlap episodes, and mortality rates. We assessed for any potential relationship between administration of a given IV vasopressor as well as vasopressor dose and EN tolerability. When assessing the relationship between presence of a given vasopressor and EN tolerability, patients were classified by whether they received the vasopressor at any time during the overlap but did not necessarily receive only that vasopressor.

Statistical Analysis

Data were analyzed using JMP Pro version 10.0.0 (SAS Institute, Cary, NC). Normality of data was assessed by visual inspection of the normal quantile plot. Normally distributed data were described using mean (standard deviation [SD]), whereas nonnormally distributed data were described with median (interquartile range [IQR]). Baseline demographic data in the study population that had objective tolerability were compared with those with objective intolerance using the χ^2 test of independence for nominal data and a 2-sample Student *t* test or Fisher exact test for continuous data. The Brown-Forsythe test was used to assess for unequal variances. If the variances were heterogeneous, Welch's analysis of variance test was used for the comparison. Multivariate logistic regression was performed to determine independent predictors of reduced EN tolerance. Factors included in the regression model were determined as those independent of one another with a probability value (*P*) of .2 or less.

Table 1. Population Demographics.

Characteristic	Overall (n = 346)	Episodes Tolerated (n = 259)	Episodes Not Tolerated (n = 87)	*P* Value[a]
Age, y, mean (SD)	57 (15.3)	56 (15.5)	58 (14.5)	.35
Male sex, No. (%)	202 (58.4)	147 (58.0)	55 (64.0)	.29
Median weight, kg (IQR)	82 (67.5–98.3)	80.9 (67.1–98)	84.4 (68.2–100.9)	.8
Etiology of hypotension, No. (%)				
Septic shock	167 (48.3)	132 (51.0)	35 (40.2)	.08
Cardiogenic shock	80 (23.1)	53 (20.5)	27 (31.0)	.048[b]
Mixed cardiogenic/septic shock	25 (7.2)	15 (5.8)	10 (11.5)	.09
Induced hypertension	23 (6.6)	16 (6.2)	7 (8.0)	.55
Hypovolemic shock	9 (2.6)	8 (3.1)	1 (1.2)	.29
Neurogenic shock	4 (1.2)	4 (1.5)	0 (0)	.13
Sedation	13 (3.8)	12 (4.6)	1 (1.2)	.1
Other mixed shock	25 (7.2)	19 (7.3)	6 (6.9)	.9
Medical service, No. (%)				
Medical ICU	164 (47.4)	127 (49.0)	37 (43.0)	.29
Cardiac surgery ICU	87 (25.1)	56 (22.0)	30 (35.0)	.0092
Neuroscience ICU	45 (13.0)	33 (13.0)	12 (14.0)	.80
Surgical/trauma ICU	21 (6.1)	18 (7.0)	3 (4.0)	.24
Coronary ICU	25 (7.2)	22 (8.0)	3 (4.0)	.12
Burn ICU	3 (0.9)	2 (1.0)	1 (1.0)	.99
Transplant ICU	1 (0.3)	1 (0.4)	0 (0)	
MAP, mm Hg, median (IQR)	74.8 (69.7–80.9)	74.8 (69.2–80.5)	74.7 (70.1–82.6)	.72
Hours of overlap, median (IQR)	31 (11.8–71.3)	26 (10–56)	65 (20–132)	.0002[b]
Feeding tube in postpyloric location, No. (%)	18 (5.2)	15 (5.8)	3 (3.4)	.57
Feeding tube in gastric location, No. (%)	328 (94.8)	244 (94.2)	84 (96.6)	.39
Median caloric density of EN product, kcal/mL (IQR)	1.5 (1–2)	1.5 (1–2)	1.5 (1–1.8)	.91
Mean prescribed calories from EN, kcal/kg/d (SD)	21.8 (6.5)	22 (6.3)	21.2 (7)	.3
Mean delivered calories from EN, kcal/kg/d (SD)	13 (7.5)	13.6 (7.6)	10.9 (6.8)	.0034[b]
Percent goal nutrition, % (IQR, %)	62.4 (34.7–87.5)	66.0 (30.5–79.0)	50 (36.3–91.8)	.0058[b]
Fentanyl equivalent, mcg/h, median (IQR)	47.9 (1.5–100)	48.3 (0.6–100)	46.7 (12.5–99.9)	.55
Concomitant inotrope, No. (%)	34 (9.8)	22 (8.5)	12 (14.0)	.15
Concomitant pentobarbital, No. (%)	9 (2.6)	7 (3.0)	2 (2.0)	.99
Concomitant paralytic, No. (%)	22 (6.4)	16 (6.0)	6 (7.0)	.81
Bowel movement, No. (%)	225 (65.0)	164 (63.0)	60 (69.0)	.25
Promotility agent, No. (%)	76 (22.0)	38 (15.0)	38 (44.0)	<.0001[b]
Oral naloxone	67 (19.4)	32 (12.0)	35 (40.0)	
Metoclopramide	13 (3.8)	8 (3.0)	4 (5.0)	
Erythromycin	4 (1.2)	0 (0)	5 (2.0)	
Any rising serum lactate, No. (%)	106 (30.6)	66 (25.5)	40 (46.0)	.0003[b]
Rising lactate >2 mmol/L, No. (%)	53 (50.0)	29 (43.9)	24 (60.0)	.12
Maximum lactate, mmol/L, median (IQR)	1.7 (1.1–2.6)	1.6 (1.05–2.4)	1.9 (1.15–2.9)	.74

EN, enteral nutrition; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial pressure.
[a]Comparison between "episodes tolerated" and "episodes not tolerated" groups.
[b]Statistically significant.

Institutional Review Board Approval

This study was approved by the Virginia Commonwealth University Institutional Review Board (Richmond, VA) as meeting criteria for expedited status. Since this was a retrospective medical record review, individual informed consent was not required.

Results

Three hundred eighty-four patients were identified for inclusion. Reasons for exclusion included ≤1-hour overlap (n = 111), pediatric patients (n = 7), and incomplete chart during the review process (n = 7). Therefore, a total of 259 patients were included with a total of 346 overlap episodes.

Table 2. Multivariate Analysis of Factors Associated With EN Tolerance.

Effect	B Estimate	χ^2	OR	95% CI	*P* Value
Hours of overlap[a]	–0.004	5.21	0.996	0.9924–0.9993	.022[b]
Etiology of hypotension					
Septic shock	0.97	0.22	1.21	0.53–2.7	.64
Cardiogenic shock	0.0052	0.00	1.01	0.4–2.52	.98
Mixed septic/cardiogenic shock	–0.166	0.32	0.72	0.23–2.33	.57
Sedation	0.688	1.47	3.96	0.6–79.42	.23
Mean delivered calories from EN, kcal/kg/d[a]	0.059	7.21	1.06	1.02–1.11	.0072[b]
Maximum norepinephrine equivalent dose ≤12.5 mcg/min	0.35	5.46	2.01	1.12–3.63	.019[b]
Concomitant inotrope	0.093	0.15	1.2	0.48–3.2	.7
Absence of a promotility agent	0.7	18	4.1	2.13–7.8	<.001[b]
Absence of any narcotic agent	–0.117	0.34	0.79	0.037–1.8	.56
Absence of any rise in serum lactate	–0.183	1.29	1.44	0.76–2.7	.26

CI, confidence interval; EN, enteral nutrition; OR, odds ratio.
[a]Per unit change in regressor.
[b]Statistically significant.

Patient characteristics are summarized in Table 1. Of the 346 overlap episodes, there were 259 cases (median 74.9%) of EN tolerance. The average blood pressure (mean arterial pressure [MAP]) during overlap was similar between groups (median 74.8 vs 74.7 mm Hg, *P* = .72). The median duration of overlap was significantly shorter in the group that tolerated EN (26 vs 65 hours, *P* = .0002). In addition, the mean caloric intake was higher in the group that had objective tolerability (13.6 vs 10.9 kcal/kg/d, *P* = .0034). Patients who tolerated EN were less likely to experience a rise in serum lactate compared with those who did not tolerate EN (25.5% vs 46.0%, *P* = .0003), but this association did not maintain statistical significance in multivariate logistic regression (Table 2). In addition, tolerability did not differ in the cohort of patients who experienced a significant rise in lactate, which was defined as a rising lactate exceeding 2 mmol/L (43.9% vs 60.0%, *P* = .12). Furthermore, the maximum lactate during overlap was similar between groups (median, 1.6 vs 1.9 mmol/L, *P* = .74). Finally, patients who tolerated EN were less likely to be prescribed a promotility agent compared with those who did not tolerate EN (15.0% vs 44.0%, *P* < .0001).

Adverse effects associated with EN intolerance are summarized in Table 3. One or more episodes of emesis or high gastric residuals (≥300 mL) occurred in 31 (9.0%) and 50 (14.5%) overlap episodes, respectively. A rising serum lactate, which can often be a nonspecific sign of ischemia, was observed in 106 (30.6%) overlap episodes, and of those, 52 (50.0%) rose to >2 mmol/L. Abdominal KUB or CT was performed in 11.9% and 4.0% of cases, respectively. We considered presence of an ileus, small bowel obstruction, or signs of bowel ischemia/perforation to be positive findings on abdominal imaging. Of patients in whom abdominal imaging was performed, 36.6% of the abdominal KUB studies and 0.9% of the abdominal CT studies had positive findings. Notably, the only positive findings on abdominal CT images were those of acute pancreatitis. Finally, there were 3 cases of bowel ischemia/perforation (summarized in Table 4).

Table 3. Adverse Events.

Adverse Event	Occurrence
≥1 Emesis, No. (%)	31/346 (9.0)
≥1 EN residual ≥300 mL, No. (%)	50/346 (14.5)
Rising serum lactate, No. (%)	106/346 (30.6)
Rising lactate >2 mmol/L, No. (%)	52/106 (50.0)
Max lactate, mmol/L, median (IQR),[a]	1.7 (1.1–2.6)
Abdominal KUB ordered, No. (%)	41/346 (11.9)
Positive findings	15/41 (36.6)
Abdominal CT ordered, No. (%)	14/346 (4.0)
Positive findings	3/346 (0.9)
Bowel ischemia/perforation, No. (%)	3/346 (0.9)

CT, computed tomography; EN, enteral nutrition; Max, maximum; IQR, interquartile range; KUB, kidney/ureter/bladder radiograph.
[a]n = 198.

A dose-response relationship was observed between maximum norepinephrine equivalent and likelihood of tolerating EN (Figure 1). Tolerability was stratified by individual IV vasopressor as well as cumulative IV vasopressor dose (Table 5). Patients who tolerated EN received a lower maximum norepinephrine equivalent dose compared with those who did not tolerate EN (12.5 vs 19.4 mcg/min, *P* = .0009).

Tolerability differed based on the vasopressor administered (Table 6). When assessing this association, patients were characterized based on having ever received a given vasopressor during the overlap, but may have received other concomitant IV vasopressors during this time. Patients who were never prescribed vasopressin during the overlap episode were more likely to tolerate EN compared with those who received vasopressin (77.9% vs 58.9%, *P* = .0027). Likewise, patients who

Table 4. Bowel Perforation Case Summaries.

Age	Sex	Weight, kg	Hours of Overlap	EN Goal Rate, mL/h	EN Product	Postpyloric Tube	Starting EN Rate, mL/hr	Mean EN Rate, mL/hr	Norepinephrine Dose at EN Initiation, mcg/min	Mean Norepinephrine Dose, mcg/min	Maximum Norepinephrine Dose, mcg/min	Stooled During Overlap	Emesis During Overlap	Residuals ≥300 mL	Rising Lactate	Mean Fentanyl Dose, mcg/h	Survival to Discharge
89	M	56	36	55	Promote	No	55	48.2	0.5	5.36	9.2	No	No	Yes	No	0	No
76	F	72	77	65	Promote; TwoCal	No	65	29.3	1.42	26	70	Yes	No	Yes	Yes	0	No
54	M	85	40	45	Pivot	No	10	25.5	11.2[a]	10[a]	11.2[a]	No	No	No	Yes	122.5	Yes

EN, enteral nutrition. Promote, TwoCal, and Pivot are manufactured by Abbott Nutrition (Columbus, OH).
[a]Patient was on 3 vasopressors (norepinephrine: initial/max dose 0.02 mcg/kg/min, mean 0.009 mcg/kg/min; epinephrine: initial/mean/max 0.05 mcg/kg/min; dopamine: initial/mean/max 7 mcg/kg/min); dose reported is in norepinephrine equivalents.

Table 5. Tolerability as a Function of Vasopressor Dose.

	Weight-Based Doses					Non–Weight-Based Doses				
	Tolerated (n = 259)		Not Tolerated (n = 87)			Tolerated (n = 259)		Not Tolerated (n = 87)		
Vasopressor	mcg/kg/min	n	mcg/kg/min	n	*P* Value	mcg/min	n	mcg/min	n	*P* Value
Norepinephrine equivalents										
Initial	0.099	259	0.11	87	.48	8.1	259	9.6	87	.25
Mean	0.085	259	0.11	87	.07	7	259	9.2	87	.048[a]
Max	0.157	259	0.23	87	.0042[a]	12.5	259	19.4	87	.0009[a]
Dopamine										
Initial	5	40	4.9	22	.89	422	40	430	22	.9
Mean	4	44	5.3	25	.11	330	44	442	25	.057
Max	6.8	44	9	25	.08	552	44	789	25	.037[a]
Epinephrine										
Initial	0.056	35	0.054	17	.77	5.3	35	5.5	17	.77
Mean	0.046	35	0.05	18	.61	4.4	35	5.1	18	.37
Max	0.067	35	0.077	18	.27	6.3	35	7.8	18	.11
Norepinephrine										
Initial	0.069	200	0.063	67	.6	5.4	200	5.4	67	.93
Mean	0.062	203	0.062	70	.98	4.9	203	5.1	70	.78
Max	0.12	203	0.143	70	.38	9.3	203	11.8	70	.13
Phenylephrine										
Initial	0.602	22	0	0		47	22	0	0	
Mean	0.538	24	0	0		44.4	24	0	0	
Max	1.04	24	0	0		85.7	24	0	0	
						units/min	n	units/min	n	*P* Value
Vasopressin										
Initial						0.035	30	0.035	16	.89
Mean						0.023	33	0.019	23	.31
Max						0.038	33	0.043	23	.35

[a]Statistically significant.

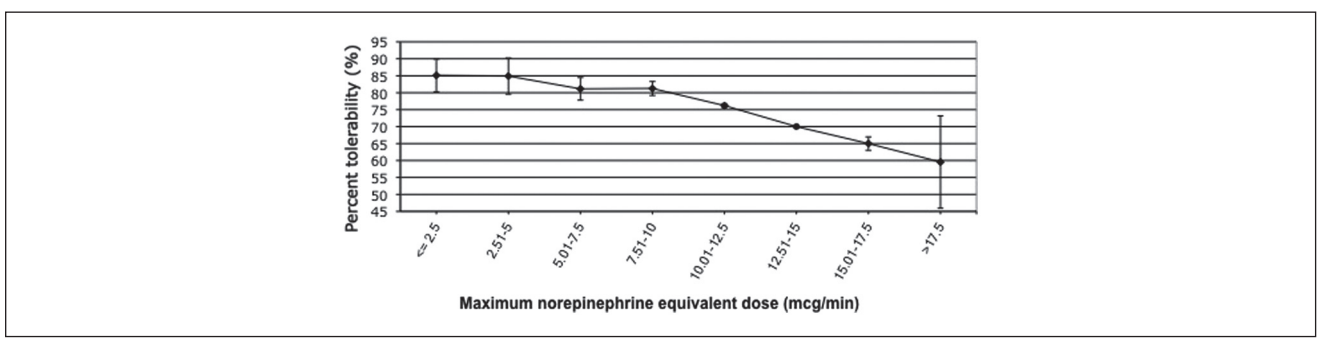

Figure 1. Percent tolerance by maximum norepinephrine equivalent dose.

Table 6. Percent Tolerability by Presence or Absence of a Given Vasopressor.

Vasopressor	Received, No. (%)	Never Received, No. (%)	*P* Value
Dopamine	44/69 (63.8)	215/277 (77.6)	.018[a]
Epinephrine	35/53 (66.4)	224/293 (76.5)	.11
Norepinephrine	203/273 (74.4)	56/73 (76.7)	.68
Phenylephrine	24/24 (100.0)	235/322 (73.0)	.0032[a]
Vasopressin	33/56 (58.9)	226/290 (77.9)	.0027[a]

[a]Statistically significant.

never received dopamine tolerated EN more frequently than those who received dopamine (77.6% vs 63.8%, $P = .018$). Neither association was consistently found to be dose related, although this subgroup analysis is likely not adequately powered (Table 5). In addition, patients who received phenylephrine were more likely to tolerate EN compared with those who did not receive phenylephrine (100.0% vs 73.0%, $P = .0023$). This finding was not dose related.

We hypothesized that EN cessation prior to discontinuation of IV vasopressor support may indicate feeding intolerance. In cases where EN was stopped prior to IV vasopressor therapy (n = 120, 34.7%), the reason for discontinuation was noted. EN intolerance accounted for 20.0% of cases. Other reasons included extubation (22.5%), increasing IV vasopressor dose (20.0%), withdrawal of care (15.0%), and procedures (13.3%).

Of the 259 patients, 167 (64.5%) survived to discharge. The most common causes of death were respiratory failure (17.4%), septic shock (13.0%), cardiopulmonary arrest (9.8%), and pneumonia (6.5%). Mortality rates did not differ based on EN tolerability. Of the 92 patients who did not survive to discharge, concomitant EN and vasopressor administration may have contributed to death in 2 cases, both of which resulted in bowel ischemia/perforation. Autopsy data were not available for the majority (94.6%) of patients not surviving to discharge; however, in a few (5.4%) cases where autopsy data were available, no bowel ischemia/perforation was identified.

Bowel Perforation Cases

An 89-year-old African American man was admitted from an outside hospital status post aystolic cardiac arrest (time to return of circulation = 9 minutes) after receiving fentanyl for pain associated with rib fractures. Upon arrival, the patient became hypotensive and bradycardic, for which he was given 1 mg epinephrine and subsequently started on a norepinephrine infusion. On day 2 of hospital admission, a Dobhoff tube was placed and an abdominal KUB revealed that the tip was in the stomach and a mild ileus present. Feeding was initiated with Promote (Abbott Nutrition, Columbus, OH) at a starting rate of 55 mL/h, which was his goal EN rate. Although at the time of EN initiation, the patient had been weaned off of norepinephrine, 2 hours after initiation of EN, norepinephrine was restarted at a low dose (0.5–6 mcg/min). On hospital day 3, the patient began to have increased distension and a slightly elevated norepinephrine requirement (8–10 mcg/min). A repeat KUB was obtained but again showed only a mild ileus. As the patient was not having increased gastric residuals and his lactate was trending down from admission, EN was continued. On hospital day 4, the patient developed lactic acidosis and worsening shock. EN was suspended and a repeat KUB revealed developing portal venous gas consistent with underlying bowel ischemia. The patient's shock rapidly progressed, and the decision was made to pursue comfort care measures. The patient expired shortly thereafter. An autopsy was not performed.

A 76-year-old African American woman with history of cerebral vascular accident with residual right-sided weakness, hypertension, diabetes, and coronary artery disease was being treated in the neuroscience ICU for status epilepticus and bacteremia. EN was initiated on hospital day 1 via an orogastric tube with Jevity (Abbott Nutrition) at 20 mL/h, which was subsequently changed to Promote (Abbott Nutrition) at a goal rate of 65 mL/h. On hospital day 4, the patient was started on pentobarbital for refractory status epilepticus. After initiation of pentobarbital, the patient's blood pressure decreased and norepinephrine was started to achieve a MAP of at least 65 mm Hg. On hospital day 5, the patient was fluid overloaded, and EN was changed to TwoCal (Abbott Nutrition) at 25 mL/h. Throughout the day, the patient became progressively more hypotensive and required escalating doses of norepinephrine. At 23:00 on hospital day 5, the patient's norepinephrine dose reached 65 mcg/min, at which time pentobarbital was held and EN suspended. The following hour, the patient's vasopressor requirement peaked at 70 mcg/min. EN was restarted the following morning, despite a downtrending but vastly elevated norepinephrine dose of 47 mcg/min and an elevated lactate (7.2 mmol/L, increased from 6.7 mmol/L the day prior). On the morning of hospital day 7, the patient had elevated gastric residuals (600 mL), prompting a KUB that showed a bowel gas pattern that could represent either small bowel obstruction or small bowel ischemia. EN was discontinued. The patient's clinical condition continued to deteriorate over the course of the next 4 days. On hospital day 10, repeat KUB revealed evidence of intra-abdominal free air, and the patient continued to have worsening hypotension despite a high-dose vasopressor. The decision was made to stop escalation of care, and the patient died on hospital day 11. An autopsy was not performed.

A 54-year-old white man with a medical history significant for heart failure and dilated cardiomyopathy (status post mitral valve replacement, internal cardiac defibrillator, and left ventricular assist device placement), hypertension, subarachnoid hemorrhage with residual seizure disorder, gastroesophageal reflux disease, and a chronic left ventricular assist device driveline infection successfully underwent orthotopic heart transplantation. On postoperative day 2, he went back to the operating room for removal of his internal cardiac defibrillator and closure of sternotomy, which was initially deferred due to significant postoperative coagulopathy. Later that evening, EN was initiated (Pivot 1.5 [Abbott Nutrition] at a rate of 10 mL/h via orogastric tube) while the patient was receiving concomitant IV vasopressor and inotropic therapies (epinephrine 0.05 mcg/kg/min, norepinephrine 0.02 mcg/kg/min, and dopamine 7 mcg/kg/min, all based on a weight of 85 kg, and isoproterenol 6 mcg/min). Over the next 28 hours, EN was advanced to a goal rate of 45 mL/h, isoproterenol was increased (8 mcg/min), and vasopressors were weaned (epinephrine 0.05 mcg/kg/min, dopamine 7 mcg/kg/min). On the afternoon of postoperative day 4, the patient was extubated and a clear liquid diet was prescribed. On postoperative day 6, the patient was noted to have brown fluid

draining from his chest tube (maximum serum lactate during feeding 2.3 mmol/L). Subsequent exploratory laparotomy revealed dense colonic adhesions in the left upper quadrant from the omentum heading toward the diaphragm. A perforation was found in the distal transverse colon that was adhered to the diaphragm, requiring transverse colectomy with colostomy. The patient experienced multiple infectious complications, including abdominal wound infection and mediastinitis, but was eventually stable for transfer back to the Veterans Administration hospital from which he came. In this case, it appears that bowel perforation was an operative complication secondary to adhesions, but was included since the etiology of the perforation could have been multifactorial.

Discussion

The primary study objective was to evaluate the tolerability of EN in critically ill patients receiving IV vasopressor therapy. Overall, we found a higher EN tolerability rate than previously reported in critically ill patients.[5] This could be attributed to changes in standard of care such as head of the bed elevation and differing thresholds for gastric residual volume. Although the definition used for objective tolerability is consistent with previous studies,[5,18,19] it has several limitations. We did not include the requirement of meeting goal nutrition into our definition of tolerability. Although a previous study examining EN tolerability included only patients receiving goal nutrition,[19] we felt that this qualifier would select for patients tolerating EN. Because we could not control for the type of EN product administered, we did not incorporate absence of diarrhea into our definition of tolerability. Diarrhea is associated with high-osmolarity EN formulas,[20] which were highly used in our cardiac population. Last, absence of a positive finding on abdominal KUB or CT was included in our composite definition of EN tolerability. Presence of an ileus is not a contraindication to EN,[21] but we postulated that patients requiring abdominal imaging were also experiencing subjective signs of intolerance (eg, distention). There were only 6 cases in which the only indicator of intolerance was a positive finding on abdominal imaging (5 of which were attributed to ileus).

The SCCM/A.S.P.E.N. guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient recommend initiation of EN within the first 24–48 hours following admission to an ICU once resuscitation and hemodynamic stability have been achieved.[1] These guidelines recommend that EN be withheld in patients requiring significant hemodynamic support, including high-dose catecholamine agents, although *high-dose* is not defined. Our study provides data that may help define "high-dose" catecholamine agents as that equivalent to 12.5 mcg/min of norepinephrine or less. Prospective trials are necessary to confirm this association.

Administration of EN to patients receiving IV vasopressor therapy appears to be reasonably safe, as the incidence of bowel ischemia/perforation was low (0.9%). Although IV vasopressor therapy may have contributed to the development of bowel ischemia/perforation, the overall incidence is similar to what is reported in the literature for spontaneous perforation in critically ill patients receiving EN.[9] It should be noted that SCCM/A.S.P.E.N. recommendations that EN be withheld in patients requiring high-dose catecholamine therapy were not followed in 1 instance of bowel perforation. This supports the need for an institution-specific EN protocol at our hospital. In our study, 64.5% of patients survived to discharge. Autopsy data were not available for the majority (94.6%) of patients who did not survive to discharge, and thus it is possible that undetected bowel ischemia may have occurred.

A secondary study objective was to identify factors associated with EN tolerance. Factors identified included a lower maximum norepinephrine equivalent dose, administration of phenylephrine, and absence of dopamine and vasopressin. Interestingly, several factors often associated with decreased EN tolerance were not found to affect EN tolerance in our study. These include use of epinephrine, absence of a bowel movement, rising serum lactate concentration, and use of opioid medications.

An inverse relationship was identified between maximum norepinephrine equivalent dose and EN tolerance (Figure 1). Although the use of an equation to calculate norepinephrine equivalents is not ideal, it allowed for an estimate of overall IV vasopressor requirement such that comparisons between groups could be made when multiple IV vasopressor agents were prescribed. As each vasopressor has different effects on splanchnic and mesenteric blood flow, further investigations of the relationship between each specific vasopressor and EN tolerance are necessary to determine a definitive dose-tolerability relationship.

The relationships between administration of a specific vasopressor and EN tolerability identified in this study, although interesting, are merely hypothesis generating. These variables were not included in the multivariate logistic regression model because receipt of each vasopressor agent was incorporated in the norepinephrine equivalent equation. Only variables independent of one another were included in the regression model. Despite this limitation, it is prudent to consider the effects of an individual vasopressor, as each agent has different effects on mesenteric vasculature.

Phenylephrine was associated with increased EN tolerance in univariate analysis. Data conflict regarding the relationship between phenylephrine and splanchnic blood flow.[22,23] In an animal model of induced septic shock, low doses of phenylephrine were associated with increased mesenteric and jejunal blood flow.[23] However, phenylephrine was associated with splanchnic vasoconstriction in a study of patients status post cardiopulmonary bypass surgery.[22] In the current study, we identified a tolerability rate of 100.0% when patients received phenylephrine; however, phenylephrine was used infrequently (n = 24). The majority (75.0%) of these patients received monotherapy with phenylephrine, and the most common indication was medically induced hypertension (37.5%) for maintenance of cerebral perfusion pressure.

The finding in univariate analysis that addition of vasopressin resulted in decreased EN tolerability is physiologically plausible. Animal and human studies indicate that vasopressin decreases mesenteric and splanchnic blood flow.[24-27] Results from studies in humans reported that vasopressin was responsible for this decreased flow even in the presence of additional catecholamines (norepinephrine).[28] We postulated that patients requiring vasopressin were experiencing refractory shock and that an increased IV vasopressor requirement alone could be driving the decrease in EN tolerance. Patients receiving vasopressin had a higher maximum IV vasopressor requirement than those who did not require vasopressin (median maximum norepinephrine equivalent dose 30 vs 7 mcg/min, $P < .001$); however, maximum norepinephrine equivalent doses were similar between those who tolerated EN and those who did not tolerate EN in this subgroup (30 vs 30 mcg/min, $P = .97$). Thus, vasopressin may be independently associated with decreased EN tolerance; however, further investigation is needed to confirm this association.

The presence of dopamine also resulted in decreased EN tolerance in univariate analysis. Although physiologic data vary,[26] dopamine has been associated with increased splanchnic oxygen requirements and decreased gastroduodenal motility.[29,30] In addition, in cardiac surgery patients, administration of dopamine is associated with decreased EN tolerance.[29,31] We hypothesized that this association could have been confounded by concomitant vasopressin use.[25] Of the 69 patients who received dopamine during their overlap episode, 21 also received vasopressin during that episode (33.9%). Although patients receiving both dopamine and vasopressin were less likely to tolerate EN compared with those who received dopamine without vasopressin, the difference was not statistically significant (52.4% vs 68.8%, $P = .19$). In addition, although patients prescribed dopamine required a higher maximum IV vasopressor dose than those who were not prescribed dopamine (maximum norepinephrine equivalent dose 12.4 vs 8 mcg/min, $P = .0043$), the maximum norepinephrine equivalent doses were similar between those who tolerated EN and those who did not tolerate EN in this subgroup (10 vs 20.7 mcg/min, $P = .08$). Hence, it appears that administration of dopamine may be independently associated with decreased EN tolerance, but this association must be confirmed with a prospective study.

Surprisingly, epinephrine was not associated with reduced EN tolerance. These data conflict as animal models suggest that epinephrine decreases mesenteric blood flow.[32] It may be the case that this finding does not translate into decreased mesenteric blood flow and/or reduced EN tolerance in humans. Furthermore, the doses of epinephrine used in our study were low, as its utilization was mostly for β-adrenergic stimulation in the post–cardiac surgery population. In our study population, EN with concurrent administration of low-dose epinephrine appeared to be safe and well tolerated.

Evidence-based guidelines state that the presence of bowel sounds and/or evidence of bowel function (passage of flatus or stool) are not required for initiation of EN.[1] Consistent with previous literature,[5] in our study, presence of a bowel movement did not predict tolerance. Presence of bowel sounds and frequency of bowel movements should continue to be monitored in patients receiving concomitant IV vasopressor therapy and EN, as decreased stool frequency and diminished bowel sounds could be early indicators of bowel ischemia.[1] Opiates, pentobarbital, and neuromuscular blockers have been associated with reduced gastric motility and decreased EN tolerance.[5,21,33-39] In our study, neither the presence nor dosage of opiate medication predicted tolerance of EN. Similarly, neuromuscular blockade and pentobarbital were not associated with decreased tolerance, though overall use of these agents was low.

In the present study, an increase in serum lactate was not associated with decreased EN tolerance. This poses a considerable dilemma when using this parameter to monitor for signs of decreasing EN tolerance in patients receiving IV vasopressor support. Trending serum lactate may have utility in early detection of bowel ischemia/perforation; however, the association between elevated serum lactate and bowel ischemia/perforation is variable. A retrospective cohort of 187 patients who underwent surgery for acute mesenteric ischemia showed that although 93.0% of patients had an elevated serum lactate, the mean lactate was only 4.2 mmol/L, along with a significant range of lactate concentrations (0.2–19 mmol/L).[40] Furthermore, lactate is an unreliable indicator of tissue ischemia in the setting of concomitant epinephrine administration, as epinephrine is independently associated with hyperlactatemia.[41-44] In our study, 38.7% of patients who experienced a rise in serum lactate were receiving concomitant epinephrine.

Patients who tolerated EN were less likely to be prescribed promotility agents. Because we classified the patient as not tolerating EN once he or she experienced a single residual ≥300 mL, it is likely that an episode of high residuals prompted prescription of promotility agents, rather than the presence of promotility agents being associated with decreased tolerance. Duration of overlap was inversely related to tolerability. As we defined tolerability as absence of any adverse event, it is logical that longer duration of therapy increases the likelihood of an adverse event.

Our study has several notable limitations. Most noteworthy is the retrospective study design and the inherent risk of selection bias. Results should be interpreted with caution, as these data are meant to be hypothesis generating and ideally would lend support for a prospective study with outcomes data. Because we looked at EN as the sole source of nutrition, patients likely received additional caloric intake, including parenteral (eg, PN, propofol, clevidipine, dextrose-containing IV solutions) or oral dietary nutrition. Hence, the percent goal nutrition, mean prescribed calories, and mean delivered calories only reflect the calories provided by EN. Other sources of nutrition were taken into account by our dietitians and the EN goal adjusted accordingly. In addition, we included multiple

ICUs to maximize generalizability. However, standard practice of EN protocols and IV vasopressor titration may have varied between ICUs and services. Last, although our study demonstrates that provision of EN to patients requiring IV vasopressor support is generally safe and well tolerated, it does not address a more fundamental question as to whether patients requiring hemodynamic support benefit from EN. Further research in this area is warranted.

To our knowledge, this is the first investigation to specifically identify a relationship between IV vasopressor agent/dose and EN tolerability. Although this study did not address timing of EN initiation (patients were included if they had an overlap of EN and IV vasopressor therapy at any time during their ICU admission), it provides important data to help the clinician stratify patients in which early EN initiation should be considered.

Conclusions

Based on our findings, EN is relatively well tolerated in patients receiving IV vasopressor support equivalent to 12.5 mcg/min of norepinephrine or less. Tolerability was less likely in patients receiving higher doses of IV vasopressors and in those receiving dopamine or vasopressin. These patients should be monitored more closely for signs of intolerance. In summary, critically ill patients receiving IV vasopressor support generally tolerate EN.

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