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Prophylactic Administration of Vasopressors Prior to Emergency Intubation in Critically Ill Patients: A Secondary Analysis of Two Multicenter Clinical Trials

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OBJECTIVE: Hypotension affects approximately 40% of critically ill patients undergoing emergency intubation and is associated with an increased risk of death. The objective of this study was to examine the association between prophylactic vasopressor administration and the incidence of peri-intubation hypotension and other clinical outcomes.

DESIGN: A secondary analysis of two multicenter randomized clinical trials. The clinical effect of prophylactic vasopressor administration was estimated using a one-to-one propensity-matched cohort of patients with and without prophylactic vasopressors.

SETTING: Seven emergency departments and 17 ICUs across the United States.

PATIENTS: One thousand seven hundred ninety-eight critically ill patients who underwent emergency intubation at the study sites between February 1, 2019, and May 24, 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was peri-intubation hypotension defined as a systolic blood pressure less than 90 mm Hg occurring between induction and 2 minutes after tracheal intubation. A total of 187 patients (10%) received prophylactic vasopressors prior to intubation. Compared with patients who did not receive prophylactic vasopressors, those who did were older, had higher Acute Physiology and Chronic Health Evaluation II scores, were more likely to have a diagnosis of sepsis, had lower pre-induction systolic blood pressures, and were more likely to be on continuous vasopressor infusions prior to intubation. In our propensity-matched cohort, prophylactic vasopressor administration was not associated with reduced risk of peri-intubation hypotension (41% vs 32%; $p = 0.08$) or change in systolic blood pressure from baseline (−12 vs −11 mm Hg; $p = 0.66$).

CONCLUSIONS: The administration of prophylactic vasopressors was not associated with a lower incidence of peri-intubation hypotension in our propensity-matched analysis. To address potential residual confounding, randomized clinical trials should examine the effect of prophylactic vasopressor administration on peri-intubation outcomes.

KEY WORDS: airway management; critical care; hypotension; intratracheal intubation; mechanical ventilation; vasoconstrictor agents

Emergency tracheal intubation has high complication rates in the emergency department (ED) and ICU (1), with approximately 40% of patients experiencing hypotension (2–10). Peri-intubation hypotension is associated with increased mortality and prolonged length of stay (2, 4, 7, 11–14).

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KEY POINTS

Question: Is prophylactic administration of vasopressors associated with less peri-intubation hypotension among critically ill adults undergoing emergency intubation?

Findings: In this U.S. multicenter cohort study, 10% of patients received prophylactic vasopressors as part of usual care prior to emergency intubation in the emergency department and ICU. There was no statistically significant difference in the incidence of peri-intubation hypotension with or without the use of prophylactic vasopressors in propensity-matched analysis (41% vs 32%, respectively).

Meaning: Due to the potential for residual confounding, a randomized clinical trial is indicated to determine whether the administration of prophylactic vasopressors prevents peri-intubation.

Whether available treatments can prevent peri-intubation hypotension remains uncertain.

In the operating room, anesthesia providers frequently administer vasopressors such as phenylephrine and ephedrine to prevent hypotension during the induction of anesthesia. This practice is effective and safe among patients undergoing elective procedures (15–21), but the efficacy of prophylactic vasopressors outside of the operating room, specifically during emergency intubation in the ED and ICU, is not well-described (22, 23).

The objective of this study was to examine the association between prophylactic vasopressor administration and the incidence of peri-intubation hypotension and other clinical outcomes. We hypothesized that the administration of prophylactic vasopressors would be associated with a lower incidence of peri-intubation hypotension during emergency intubation in the ED and ICU.

MATERIALS AND METHODS

We conducted a post hoc analysis of data from two multicenter, randomized clinical trials in the United States (Bougie or Stylet in Patients Undergoing Intubation Emergently [BOUGIE] and Preventing Cardiovascular Collapse With Administration of Fluid Resuscitation During Induction and Intubation [PREPARE II] that, together, enrolled 1,873 patients undergoing emergency intubation in the ED and ICU between February 1, 2019, and May 24, 2021 (24, 25). Briefly, the BOUGIE trial evaluated the use of bougie versus stylet on first-attempt success and PREPARE II investigated the effect of pre-induction IV crystalloid fluid bolus on preventing cardiovascular collapse after intubation. In both trials, the decision to administer prophylactic vasopressors was based on clinician discretion as part of clinical care. Both studies were conducted by the Pragmatic Critical Care Research Group in the United States using the same data collection methods. This secondary analysis was approved by the Colorado Multiple Institutional Review Board (No. 21-4847, November 19, 2021, Hypotension Following Emergency Intubation in Critically Ill Patients). Waiver of Consent was granted by the Colorado Multiple Institutional Review Board. All procedures followed the ethical standards of the institutional committee and the Helsinki Declaration of 1975. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology statement (26).

Participants

Twenty-four sites participated in the parent trials, including seven EDs and 17 ICUs (medical, surgical, and neurologic) across the United States. Patients were eligible if they were adults (≥ 18 yr) undergoing tracheal intubation at the study sites with planned use of sedation. Patients were excluded if they were pregnant, incarcerated, had an immediate need for intubation such that study procedures were not possible, or were determined to have either an indication for or contraindication to the parent study interventions (i.e., bougie or fluid bolus). For this secondary analysis, we excluded patients who had cardiac arrest preceding emergency intubation.

Data Collection

Research personnel collected data on patient demographics, comorbidities, indications for intubation, active medical conditions (neurologic, cardiac, pulmonary, gastrointestinal, sepsis, trauma, and COVID-19), Acute Physiology and Chronic Health Evaluation II (APACHE II) score (27), use of vasopressor infusions prior to enrollment, and clinical outcomes. In addition, a trained, independent observer recorded

data on the intubation procedure (fluid bolus administration, pre-oxygenation device, choice of sedation, oxygenation and ventilation between induction and laryngoscopy, number of attempts at intubation, and administration of prophylactic vasopressors) and peri-procedural vitals (peripheral arterial oxygen saturation and systolic blood pressure at induction [baseline] and the lowest measured values from the time of induction until 2 min following successful intubation).

Definition and Outcome Measures

The primary exposure of interest, prophylactic vasopressor administration, was defined as the administration of a vasopressor bolus or dose increase immediately prior to or at induction of anesthesia. As prophylactic vasopressors were administered as part of routine clinical care, clinicians determined the choice of vasopressor and its dose. The administration (whether delivered as a bolus or dose increase of existing infusion) was concurrent with the induction agent without titration. This predefined prophylactic vasopressor administration was recorded systematically in the prospective, bedside research data collection form.

The primary outcome was peri-intubation hypotension defined as any systolic blood pressure less than 90 mm Hg between the time of induction and 2 minutes after successful intubation of the trachea. This relatively narrow time window was chosen in the parent trials to evaluate the blood pressure change due to the procedure without the influence of post-intubation management such as initiation of mechanical ventilation and continuous sedative infusion. Secondary outcomes included change in systolic blood pressure from baseline to lowest (ΔSBP), new initiation or dose increase of vasopressor infusion to treat hypotension following induction, cardiac arrest within 1 hour of the intubation, 30-day in-hospital mortality, duration of mechanical ventilation, and ICU length of stay. We used the sepsis definition described in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) to define sepsis (28).

Statistical Analysis

As a secondary analysis of a dataset of fixed size, a sample size estimation was not performed. We summarized continuous variables as means (SD) or medians (interquartile range) and compared them using the Student *t* test or Wilcoxon rank-sum test as appropriate based on the distribution. Categorical variables were expressed as numbers (percentages) and compared using the Fisher exact test. We performed univariate analyses to compare baseline and procedural factors between patients with and without prophylactic vasopressors in the overall cohort. Missing data were handled with pairwise deletion, given limited missing values in the dataset.

To minimize confounding due to indication (i.e., factors associated with receiving prophylactic vasopressors driving the outcome) and other pretreatment conditions, we derived a propensity-matched cohort in which patients who received prophylactic vasopressors were matched one-to-one based on the conditional probability of receiving prophylactic vasopressors. The propensity score model used optimal regression adjusting for the following 13 covariates, selected based on the literature (8, 10, 29, 30) and our clinical knowledge: age, history of hypertension, history of chronic kidney disease, APACHE II score, sepsis diagnosis, presence of trauma, COVID-19 diagnosis, pre-induction oxygen saturation, pre-induction systolic blood pressure, pre-enrollment receipt of vasopressor infusions, induction agent, receipt of bag-mask ventilation between induction and intubation, and enrollment in PREPARE II. When selecting pretreatment variables to construct propensity scores, our goal was to include as many covariates related to treatment assignment and outcome as possible since there is no statistical harm in adjusting for variables that may not be true confounders (31). We did not include covariates unrelated to treatment assignment or outcome. The propensity-matched cohort consisted of 187 patients who received prophylactic vasopressors and 187 patients who did not receive prophylactic vasopressors, for a total sample size of 374. We calculated the standardized mean differences (SMDs) to evaluate the balance of covariates between the two groups, using an absolute value of less than 0.1 as the threshold for satisfactory balance.

We analyzed ventilator-free days and ICU-free days in the propensity-matched cohort using hurdle models including prophylactic vasopressor administration as the only predictor. Ventilator-free days and ICU-free days were defined as the number of calendar days between enrollment (= emergency intubation) and 28 days after enrollment on which the patient was alive and not receiving mechanical ventilation or not in the

ICU, respectively. Patients who died before day 28 received a value of zero. The first step of the hurdle model evaluated whether the subject had more than zero x-free days using logistic regression where odds ratios (ORs) greater than one indicate that prophylactic vasopressor administration increased the odds of having 1 less than or equal to x-free days. In the second step, we used Poisson regression to evaluate the count of x-free days conditional on the subject having 1 less than or equal to x-free days. Rate ratios (RRs) greater than one indicate more x-free days in the prophylactic vasopressor group.

Log-rank tests were used to assess whether 30-day survival after emergency intubation differed by prophylactic vasopressor exposure in the propensity-matched cohort. Those who were not dead at or before 30 days peri-intubation were right-censored.

Multivariable logistic regression evaluated the association between peri-intubation systolic blood pressure and 30-day mortality in the overall cohort, adjusting for age, APACHE II score, sepsis diagnosis, pre-induction systolic blood pressure, pre-enrollment receipt of vasopressor infusions, and induction agents. All analyses were carried out using R Version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overview of the Entire Cohort

Of 1,873 patients in the trial datasets, we excluded 75 with cardiac arrest preceding intubation, resulting in 1,798 included in the analysis. The mean age was 58 ± 16 years, and 1,048 (58%) were male. Approximately one-third of intubations took place in the ED and two-thirds in the ICU, and 88% of all intubations were performed by residents and fellows (**Table 1**). A total of 187 patients (10%) received prophylactic vasopressors. A total of 299 patients (17%) experienced peri-intubation hypotension, and 620 died (34%) within 30 days of emergency intubation.

Characteristics of Patients Who Received Prophylactic Vasopressors

As compared with patients who did not receive prophylactic vasopressors, patients who received prophylactic vasopressors were older (61 vs 57 yr old; $p = 0.002$), had higher APACHE II scores (22 vs 17; $p < 0.001$), had a higher prevalence of sepsis (73% vs 42%; $p < 0.001$), and were less likely to have a diagnosis of trauma (1% vs 10%; $p < 0.001$) (Table 1).

The administration of prophylactic vasopressors was more common in the ICU compared with the ED (12% vs 7%; $p < 0.001$). Patients who were treated with prophylactic vasopressors were more likely to be on vasopressor infusions prior to enrollment (55% vs 10%; $p < 0.001$) and had a lower pre-induction systolic blood pressure (110 vs 135 mm Hg; $p < 0.001$) (**Table 2**).

Propensity Score-Matched Cohort Balance Assessment

The propensity score-matched cohort included 374 patients, 187 in the prophylactic vasopressors group and 187 in the no prophylactic vasopressors group. The following covariates did not meet absolute SMD less than 0.1 by small margins: the prevalence of chronic obstructive pulmonary disease (SMD = –0.106), cerebrovascular accident (SMD = –0.103), trauma diagnosis (SMD = –0.119), and operator previous intubation experience (SMD = 0.114). We observed the greatest imbalance between the two groups in total fluid bolus (SMD = 0.196) with median administered volumes of 125 and 2.5 mL for the prophylactic vasopressor group and the no prophylactic vasopressor group, respectively ($p = 0.25$). Despite the significant overlap between our study period and the COVID-19 pandemic, each group in our matched cohort included only 8% with COVID-19 diagnosis and were well-balanced (SMD = –0.019) (Tables 1 and 2; and **eFig. 1**, http://links.lww.com/CCX/B220).

Effect of Prophylactic Vasopressors in the Propensity Score-Matched Cohort

The incidence of peri-intubation hypotension (primary outcome) did not differ between patients with and without the administration of prophylactic vasopressors in the propensity-matched cohort (41% vs 32%; $p = 0.08$). For secondary outcomes, we found no between-group differences in ΔSBP (–12 vs –11 mm Hg; $p = 0.66$), cardiac arrest within 1 hour (4% vs 3%; $p = 0.77$), or 30-day mortality (57% vs 47%; $p = 0.08$). Patients who received prophylactic vasopressors had a higher rate of new initiation or dose increase of vasopressor infusion to treat hypotension (40% vs 29%; $p = 0.03$) (**Table 3**). Prophylactic vasopressor administration was not associated with ventilator-free days (step 1: OR, 0.75; 95% CI, 0.50–1.14; $p = 0.18$ and step 2: RR, 0.99; 95% CI, 0.93–1.05; $p = 0.71$) or ICU-free

TABLE 1.
Baseline Characteristics

Characteristics	Overall Cohort			Propensity-Matched Cohort		
	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 1,611)	*p*	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 187)	*p*
Age (yr)	61 ± 15	57 ± 16	0.002[d]	61 ± 15	61 ± 15	0.65[d]
Sex (male)	104 (56%)	944 (59%)	0.44	104 (56%)	96 (51%)	0.47
Race						
White	131 (70%)	1,127 (70%)	0.87	131 (70%)	123 (66%)	0.44
African American	45 (24%)	348 (22%)	0.52	45 (24%)	51 (27%)	0.48
Asian	6 (3%)	29 (2%)	0.26	6 (3%)	6 (3%)	> 0.99
Other[b]	5 (3%)	89 (6%)	0.12	5 (3%)	6 (3%)	0.77
Hispanic	12 (6%)	123 (8%)	0.66	12 (6%)	14 (8%)	0.84
Body mass index (kg/m^2)	29.2 ± 8.7	28.4 ± 8.1	0.44[e]	29.2 ± 8.7	29.0 ± 8.1	0.56[e]
Hypertension	57 (31%)	562 (35%)	0.26	57 (31%)	60 (32%)	0.82
Congestive heart failure	31 (17%)	184 (11%)	0.04	31 (17%)	33 (18%)	0.89
Coronary artery disease	22 (12%)	183 (11%)	0.90	22 (12%)	26 (14%)	0.64
Atrial fibrillation	23 (12%)	173 (11%)	0.54	23 (12%)	28 (15%)	0.55
Chronic obstructive pulmonary disease	24 (13%)	264 (16%)	0.25	24 (13%)	31 (17%)	0.38
Obstructive sleep apnea	10 (5%)	106 (7%)	0.64	10 (5%)	10 (5%)	> 0.99
Cerebrovascular accident	11 (6%)	127 (8%)	0.39	11 (6%)	16 (9%)	0.43
Diabetes mellitus	45 (24%)	373 (23%)	0.78	45 (24%)	54 (29%)	0.35
Chronic kidney disease	19 (10%)	153 (10%)	0.79	19 (10%)	18 (10%)	> 0.99
End-stage renal disease	15 (8%)	65 (4%)	0.02	15 (8%)	14 (8%)	> 0.99
Cirrhosis	33 (18%)	210 (13%)	0.09	33 (18%)	37 (20%)	0.69
Indications for intubation			0.008			0.62
Acute respiratory failure	93 (50%)	720 (45%)		93 (50%)	98 (52%)	
Altered mental status	59 (32%)	631 (39%)		59 (32%)	56 (30%)	
Emergency procedure	11 (6%)	118 (7%)		11 (6%)	16 (9%)	
Hemodynamic instability	9 (5%)	21 (1%)		9 (5%)	8 (4%)	
Other	15 (8%)	121 (8%)		15 (8%)	9 (5%)	
Acute Physiology and Chronic Health Evaluation II	22 (17–28)	17 (12–22)	< 0.001[d]	22 (17–28)	23 (16–28)	0.80[d]
Glasgow Coma Scale	12 (8–15)	12 (7–15)	0.50[e]	12 (8–15)	12 (8–14)	0.82[e]
Sepsis[c]			< 0.001			0.72
Sepsis	54 (29%)	479 (30%)		54 (29%)	47 (25%)	
Septic shock	82 (44%)	186 (12%)		82 (44%)	87 (47%)	
Active cardiac conditions			0.25			0.54
Heart failure	7 (4%)	44 (3%)		7 (4%)	8 (4%)	
Acute coronary syndrome	6 (3%)	31 (2%)		6 (3%)	4 (2%)	
Cardiogenic shock	4 (2%)	15 (1%)		4 (2%)	5 (3%)	

(*Continued*)

TABLE 1. (*Continued*)
Baseline Characteristics

Characteristics	Overall Cohort			Propensity-Matched Cohort		
	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 1,611)	*p*	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 187)	*p*
Gastrointestinal bleeding	26 (14%)	148 (9%)	0.05	26 (14%)	28 (15%)	0.88
Trauma admission	2 (1%)	167 (10%)	< 0.001	2 (1%)	5 (3%)	0.45
COVID-19	14 (8%)	63 (4%)	0.03	14 (8%)	15 (8%)	> 0.99

[a]Prophylactic administration of vasopressor bolus or dose increase prior to or at induction.
[b]Other race included native American, native Hawaiian, and Pacific Islander.
[c]Sepsis was defined following the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (28).
[d]*p* value from *t* test.
[e]*p* value from Wilcoxon rank-sum test.
Values are expressed as mean ± SD, median (interquartile range), and count (%).

days (step 1: OR, 0.82; 95% CI, 0.55–1.24; $p = 0.35$ and step 2: RR, 0.94; 95% CI, 0.88–1.01; $p = 0.11$). In log-rank test, patients treated with prophylactic vasopressors had a higher mortality at 30 days after emergency intubation (hazard ratio, 1.37; 95% CI, 1.03–1.81; $p = 0.03$) (**Fig. 1**).

Since more than half of patients in our propensity-matched cohort were already receiving vasopressor infusions prior to enrollment (Table 2), we examined the clinical effects of prophylactic vasopressor administration in the propensity-matched subcohort of 168 patients without a pre-enrollment vasopressor receipt (32). In this post hoc subgroup analysis, we found no differences in peri-intubation hypotension, ΔSBP, or new initiation of vasopressors (**eTable 1**, http://links.lww.com/CCX/B220). Patients who received prophylactic vasopressors had a higher hazard ratio for 30-day mortality in log-rank test ($p = 0.04$) (**eFig. 2**, http://links.lww.com/CCX/B220).

Peri-Intubation Hypotension and 30-Day Mortality (Overall Cohort)

Baseline characteristics, procedural management, and outcomes of patients with and without peri-intubation hypotension in the overall cohort are detailed in **eTables 2–4** (http://links.lww.com/CCX/B220). In multivariable logistic regression analysis, we found a linear association between the lowest recorded peri-intubation systolic blood pressure and 30-day mortality; the odds of 30-day mortality increased by 8% with every 10 mm Hg decrease in the peri-intubation systolic blood pressure (OR, 1.08; 95% CI, 1.03–1.12; $p = 0.001$). There was a similar association between ΔSBP and the risk of 30-day mortality (OR, 1.08; 95% CI, 1.03–1.12; $p = 0.001$) (**Fig. 2**).

DISCUSSION

In this secondary analysis of 1,798 patients undergoing emergency intubation at 24 sites across the United States, peri-intubation hypotension was associated with an increased risk of 30-day mortality. Prophylactic vasopressors were administered to 10% of critically ill patients prior to intubation. In our propensity-matched cohort consisting of 374 patients, the administration of prophylactic vasopressors was not associated with a lower incidence of peri-intubation hypotension.

The lack of prophylactic vasopressor administration's effect on peri-intubation hypotension was contrary to our hypothesis and unexpected given that bolus dose vasopressors have been shown to reduce hypotension in the setting of elective intubation in the operating room (15–21) and increase systolic blood pressure among critically ill patients in the ED (33) and ICU (34). Our definition of prophylactic vasopressors included two distinct interventions: 1) administration of bolus dose prophylactic vasopressors in patients not on vasopressors infusions prior to enrollment and 2) bolus dose or increasing the dose of vasopressors in patients already receiving vasopressor infusions prior to enrollment. To isolate the effects of new vasopressor administration, we performed a post hoc sensitivity analysis among patients who were not on vasopressor infusions prior to enrollment, but the results remained similar.

TABLE 2.
Procedural Management

Variables	Overall Cohort			Propensity-Matched Cohort		
	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 1,611)	*p*	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 187)	*p*
Intubation location			< 0.001			0.80
Emergency department	41 (22%)	575 (36%)		41 (22%)	39 (21%)	
ICU	143 (77%)	1,012 (63%)		143 (77%)	146 (78%)	
Operator specialty			< 0.001			0.96
Emergency medicine	45 (24%)	617 (38%)		45 (24%)	46 (25%)	
Critical care	129 (69%)	908 (56%)		129 (69%)	128 (68%)	
Anesthesiology	11 (6%)	60 (4%)		11 (6%)	9 (5%)	
Other	2 (1%)	23 (1%)		2 (1%)	3 (2%)	
Operator level of training			0.35			0.10
Resident/fellow	171 (91%)	1,420 (88%)		171 (91%)	160 (86%)	
Attending physician	9 (5%)	84 (5%)		9 (5%)	10 (5%)	
Advanced practice provider[b]	7 (4%)	104 (7%)		7 (4%)	17 (9%)	
Operator previous intubation experience	50 (30–90)	55 (30–90)	0.88[i]	50 (30–90)	50 (30–80)	0.54[i]
Baseline oxygen saturation (%)[c]	99 (94.5–100)	100 (97–100)	0.004[i]	99 (94.5–100)	99 (95–100)	0.29[i]
Pre-induction oxygenation			0.71			0.74
High-flow nasal cannula	31 (17%)	240 (15%)		31 (17%)	30 (16%)	
Bilevel positive pressure ventilation	44 (24%)	345 (21%)		44 (24%)	50 (27%)	
F_{IO_2} prior to intubation	0.50 (0.24–0.90)	0.50 (0.27–0.80)	0.75[i]	0.50 (0.24–0.80)	0.50 (0.27–0.90)	0.75[i]
Baseline systolic blood pressure (mm Hg)[c]	110 ± 24	135 ± 30	< 0.001[h]	110 ± 24	111 ± 21	0.66[h]
Vasopressor infusion prior to enrollment[d]	103 (55%)	167 (10%)	< 0.001	103 (55%)	97 (52%)	0.60
Norepinephrine	91 (49%)	148 (9%)		91 (49%)	86 (46%)	
Phenylephrine	14 (8%)	20 (1%)		14 (8%)	15 (8%)	
Epinephrine	10 (5%)	16 (1%)		10 (5%)	9 (5%)	
Dopamine	1 (0.5%)	1 (0.1%)		1 (0.5%)	0 (0%)	
Angiotensin II	2 (1%)	2 (0.1%)		2 (1%)	2 (1%)	
Induction agents						
Propofol	17 (9%)	106 (7%)	0.22	17 (9%)	17 (9%)	> 0.99
Etomidate	134 (72%)	1,168 (73%)	0.80	134 (72%)	131 (70%)	0.82
Ketamine	35 (19%)	312 (19%)	0.92	35 (19%)	33 (18%)	0.89
Bag-mask ventilation between induction and intubation	118 (63%)	878 (55%)	0.03	118 (63%)	114 (61%)	0.75
First-attempt success[e]	157 (84%)	1,346 (84%)	> 0.99	157 (84%)	152 (81%)	0.59

(*Continued*)

TABLE 2. (*Continued*)
Procedural Management

Variables	Overall Cohort			Propensity-Matched Cohort		
	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 1,611)	*p*	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 187)	*p*
Duration of intubation (s)[f]	130 (96–190)	129 (97–187)	0.79[i]	130 (96–190)	120 (97–180)	0.40[i]
Lowest oxygen saturation (%)[g]	96 (87–100)	97 (88–100)	0.07[i]	96 (87–100)	96 (89–100)	0.71[i]
Fluid bolus						
Pre-induction (mL)	63.5 (0–269)	0 (0–250)	0.22[i]	63.5 (0–269)	0 (0–300)	0.44[i]
Total (mL)	125 (0–500)	7.5 (0–450)	0.16[i]	125 (0–500)	2.5 (0–423)	0.25[i]
Enrolled in BOUGIE (24)	94 (50%)	935 (58%)	0.05	94 (50%)	95 (51%)	> 0.99
Enrolled in PREPARE II (25)	127 (68%)	933 (58%)	0.009	127 (68%)	125 (67%)	0.91

BOUGIE = The Bougie or Stylet in Patients Undergoing Intubation Emergently trial, PREPARE II = Preventing Cardiovascular Collapse With Administration of Fluid Resuscitation During Induction and Intubation trial.
[a]Prophylactic administration of vasopressor bolus or dose increase prior to or at induction.
[b]Advanced practice providers included physician assistants, certified registered nurse anesthetists, and nurse practitioners.
[c]Baseline peripheral arterial oxygen saturation and systolic blood pressure were measured at the time of induction.
[d]Any vasopressor or inotropic infusion(s) in the hour prior to enrollment.
[e]First-attempt success was defined as a single insertion of a laryngoscope blade into the mouth and passage of endotracheal tube into the trachea.
[f]Time from induction to successful endotracheal tube placement in seconds.
[g]Lowest peripheral arterial oxygen saturation recorded between induction and 2 min of successful intubation.
[h]*p* value from *t* test.
[i]*p* value from Wilcoxon rank-sum test.
Values are expressed as mean ± SD, median (interquartile range), and count (%).

TABLE 3.
Outcomes in the Propensity-Matched Cohort

Outcomes	Propensity-Matched cohort		*p*
	Vasopressor[a] (*n* = 187)	No Vasopressor (*n* = 187)	
Peri-intubation hypotension[b]	76 (41%)	60 (32%)	0.08
Change in systolic blood pressure[c]	−12 ± 23	−11 ± 22	0.66[e]
New initiation of vasopressors[d]	75 (40%)	54 (29%)	0.03
Cardiac arrest within 1 hr	7 (4%)	5 (3%)	0.77
30-d mortality	106 (57%)	88 (47%)	0.08

[a]Prophylactic administration of vasopressor bolus or dose increase prior to or at induction.
[b]Systolic blood pressure < 90 mm Hg recorded between induction and 2 min of successful intubation.
[c]Calculated as follows: (lowest systolic blood pressure recorded between induction and 2 min of successful intubation)−(systolic blood pressure measured at the time of induction).
[d]New or increased vasopressors between induction and 2 min of successful intubation.
[e]*p* value from *t* test.
Values are expressed as mean ± SD, median (interquartile range), and count (%).

There are several potential explanations for the lack of hemodynamic effects observed in this study. First, we did not have data on vasopressor choice or dose to evaluate the impact of different vasopressor agents and administration techniques. Second, although our propensity-matched cohort was well-balanced in

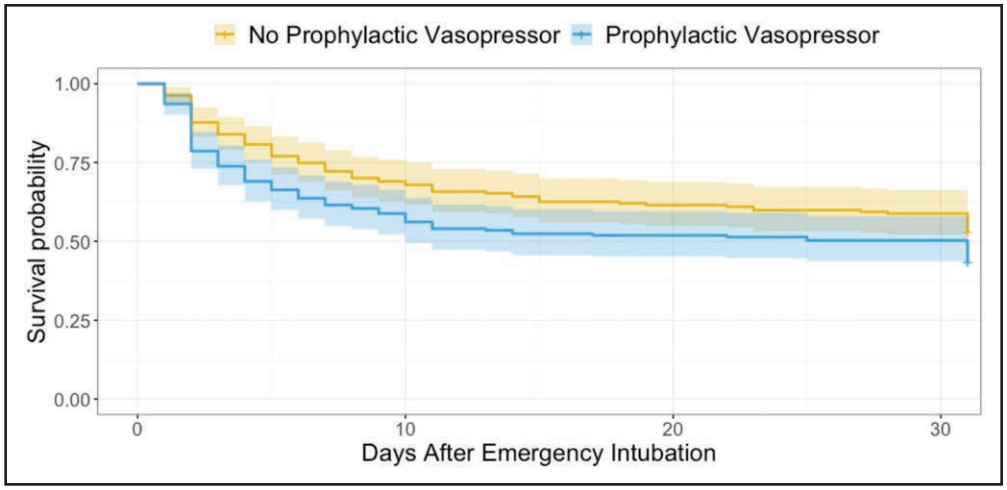

Figure 1. Kaplan-Meier curve of 30-d survival from the time of emergency intubation in the propensity-matched cohort (374 patients). The difference in survival curves by prophylactic vasopressor exposure was statistically significant in log-rank test (hazard ratio, 1.37; 95% CI, 1.03–1.81; $p = 0.03$).

most measured variables, patients who received prophylactic vasopressors had a higher hazard ratio for death 30 days after emergency intubation. In addition, we found marked differences in the characteristics of patients who did and did not receive prophylactic vasopressors prior to propensity matching. This raises the possibility that patients who received prophylactic vasopressors had residual confounding from indications that rendered them at higher risk for poor outcomes. Since it is unlikely that prophylactic vasopressor administration is harmful among critically ill patients undergoing emergency intubation, we believe that the need for vasopressors may be related to the disease severity and avoidance of prophylactic vasopressors may have only exacerbated the subsequent hypotension and the risk of peri-intubation cardiac arrest.

A recent study by Russotto et al (35) also investigated modifiable factors associated with cardiovascular collapse with intubation occurring outside of the operating room. In this secondary analysis of a multicenter cohort study, vasopressors administered before induction were not associated with a reduced incidence of cardiovascular instability or collapse. Our study leveraged more recent data rigorously collected from prospective clinical trials and defined hemodynamic instability differently, but the main findings were similar to those of Russotto

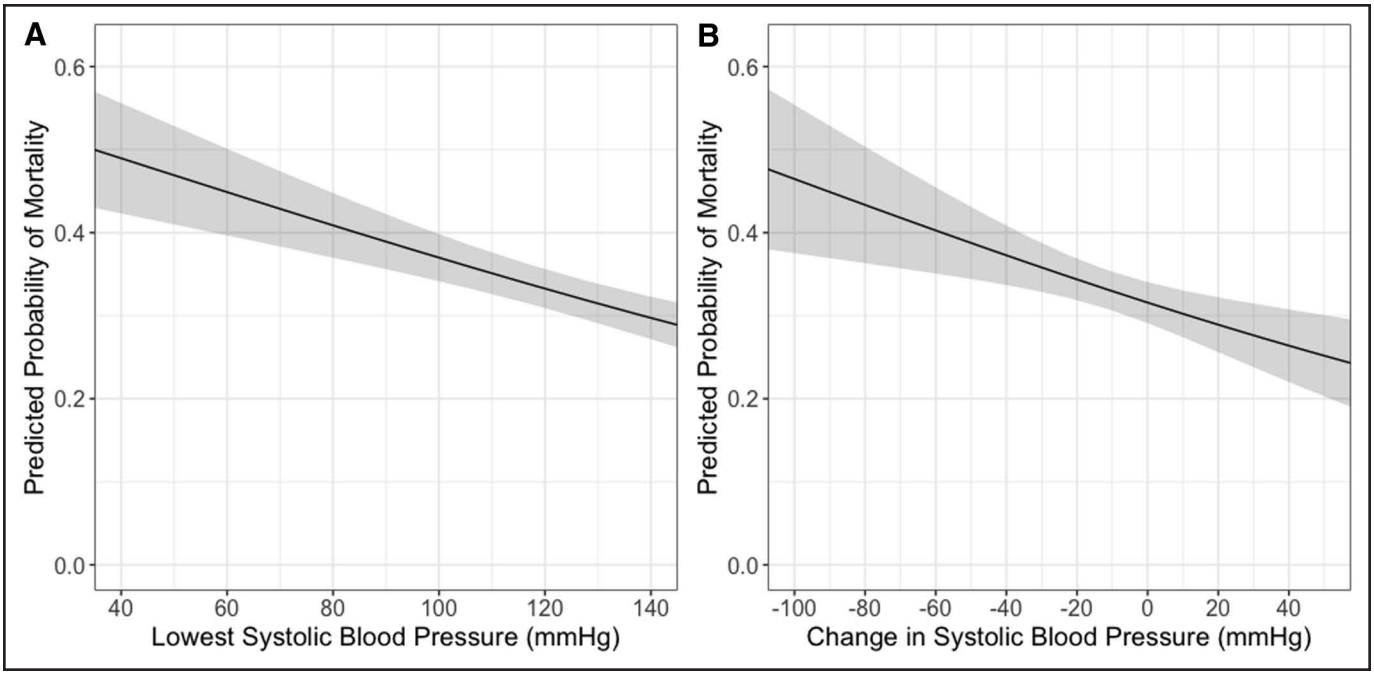

Figure 2. Predicted probability of 30-d mortality by peri-intubation systolic blood pressures measured between induction and 2 min of successful intubation. Both the lowest systolic blood pressure (**A**) and change in systolic blood pressure from pre-induction baseline (**B**) were independently associated with an increased risk of 30-d mortality. The analyses included the overall cohort of 1,798 patients.

et al (35). Both studies acknowledge the effects of residual confounding in the analyses—this key issue would be best addressed by future randomized trials.

We found that only 10% of patients received prophylactic vasopressors prior to emergency intubation. Two previous studies reported similar figures—14% in an ED (36) and 13% in a medical ICU (37). The ED study also showed that septic patients were more likely to receive prophylactic vasopressors than nonseptic patients (36), which was consistent with our findings. In our study, patients who received prophylactic vasopressors were also older, had higher severity of illness scores, had lower pre-induction systolic blood pressures, and were more likely to be receiving vasopressor infusions before intubation. These characteristics match previously described risk factors for peri-intubation hypotension (8, 10–12, 29, 30, 38), suggesting that clinicians tend to administer prophylactic vasopressors to patients assessed to be at higher risk of experiencing peri-intubation hypotension. Future study designs may benefit from using these factors for prognostic enrichment (39).

The association between peri-intubation hypotension and mortality was also consistent with prior studies (2, 4, 7, 11–14). Whether preventing peri-intubation hypotension would reduce mortality remains unknown (23). In addition to administering prophylactic vasopressors, two other interventions have been tested to decrease the risk of per-intubation hypotension: choice of induction agent and administration of an IV fluid bolus. In a recent trial comparing etomidate versus ketamine for induction of emergency intubation, etomidate was associated with a reduced incidence of cardiovascular collapse but had no statistically significant impact on 28-day survival (40). The use of induction agents (etomidate, ketamine, and propofol) was similar between groups in our propensity-matched cohort. Although an early observational study by Jaber et al (41) suggested a lower incidence of cardiovascular collapse when a pre-induction fluid bolus was administered as part of a care bundle, two subsequent randomized clinical trials found that an IV fluid bolus did not prevent hypotension during emergency intubation (25, 42).

Our study has several limitations. First, our definition of prophylactic vasopressors was broad and lacked details such as the choice of vasopressor agent, dose, administration methods (bolus vs infusion), and use of a blood pressure target. Future research should evaluate the effect of different vasopressor administration strategies (31, 43). Second, the median duration of blood pressure measurement was 4–5 minutes after induction. This was shorter than in most previous studies, which measured up to 60 minutes after intubation (5, 7, 9, 12, 14, 29, 30, 36, 44). Therefore, our study could not evaluate the hemodynamic effect of prophylactic vasopressors beyond 2 minutes after successful intubation, but we believe that the narrower time window is more likely to reflect the hemodynamic effects of the procedure itself (and the administration of prophylactic vasopressors given their rapid onset of action) rather than subsequent interventions such as initiation of mechanical ventilation and continuous sedatives. Third, our study data did not include the modality or frequency of blood pressure measurement. These data may be important because noninvasive blood pressure measurement using an oscillometric cuff has been shown to overestimate low arterial blood pressure (45), and the frequency of blood pressure measurements has been associated with the detection of hypotension (46–49). Fourth, we did not have data on the dose of induction agents to account for their dose-dependent effects on blood pressure. Fifth, although the overall first-pass success rate (84%) was comparable to a meta-analysis of ED intubation (50), most intubations were performed by trainees, so our study findings may not apply to nonteaching hospitals. Last, despite the large sample size, rigorous data collection, and propensity score analysis, our data suggest that clinicians were more likely to administer prophylactic vasopressors in patients at higher risk for peri-intubation hypotension. We cannot rule out the effects of residual confounding due to unmeasured factors such as cardiac function, fluid status, and induction agent dosage.

CONCLUSIONS

In this U.S. multicenter study, 10% of critically ill patients received prophylactic vasopressors as part of usual care prior to emergency intubation in the ED and ICU. Prevention of peri-intubation hypotension is likely important given its strong association with 30-day mortality. However, in a propensity-matched analysis, the administration of prophylactic vasopressors was not associated with a lower incidence of peri-intubation hypotension. To address potential residual

confounding, a randomized clinical trial should examine the effect of prophylactic vasopressor administration on peri-intubation outcomes.

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Drs. Fuchita and Ginde conceived and designed the study. Drs. Fuchita, Pattee, Williamson, Semler, and Casey had full access to the data used in this study and are responsible for their integrity. Dr. Fuchita, Pattee, and Williamson were involved in the data analysis. Drs. Fuchita and Pattee wrote the initial article draft. All authors contributed substantially to the study design, data acquisition, data interpretation, or a combination thereof. All authors critically reviewed and revised the article and approved the final version for publication.

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