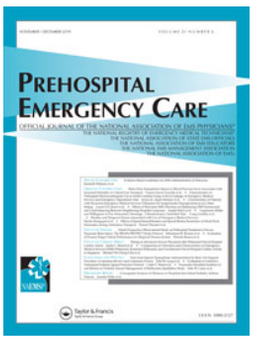

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Original Contributions

Bolus Dose Epinephrine Improves Blood Pressure but is Associated with Increased Mortality in Critical Care Transport

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Abstract

Objective: Hypotension in the prehospital environment is common and linked to dose-dependent mortality. Bolus dose epinephrine (BDE) may reverse hypotension. We tested if BDE use to treat profound hypotension is associated with 24-hour survival. **Methods:** We performed a retrospective case-cohort study of critical care transport patients with systolic blood pressure (SBP) <70 mmHg from January 2011 to January 2017. To account for baseline differences between treated and untreated patients, we used nearest neighbor matching to estimate the average treatment effect of BDE on 24-hour survival. Included covariates were age, gender, shock type (cardiogenic, distributive, obstructive or hypovolemic), weight, type of service, vitals (heart rate, SBP and diastolic blood pressure, respiratory rate, oxygen saturation, end-tidal carbon dioxide, and Glasgow Coma Scale score) at the time of the first hypotensive episode, as well as pretreatment characteristics including cardiopulmonary resuscitation, defibrillation, transcutaneous pacing, needle thoracostomy, vasopressors, intubation, or arrhythmias. After statistical analysis, we assessed for residual bias by selecting random matched patient records and asking 2 blinded physicians to rate overall illness severity on a Likert scale. We compared perceived illness severity between cases and matched controls using a rank-sum test. **Results:** There were 6,992 patients transported with SBP <70 mmHg at least once and 4,374 meet inclusion criteria. Of the 1,620 patients transported after protocol implementation, 574 (35%) received BDE. Overall 24-hour survival, survival to discharge and 30-day survival were 80, 57, and 54%, respectively. Survival at 24 hours differed between the BDE group (66%) and controls (82%). These differences persisted at both discharge and 30 days. Administration of BDE was associated with increased post-treatment SBP. BDE treated patients were also more likely to receive cardiopulmonary resuscitation and vasopressors after treatment than untreated hypotensive patients, but there was no association with tachydysrhythmias requiring defibrillation. **Conclusions:** Bolus dose epinephrine increases blood pressure in the prehospital setting. Despite robust efforts to control for confounding, BDE remained associated with increased mortality in this observational cohort. This association may be due to unmeasured confounding and a randomized controlled trial is necessary to establish a causal relationship between bolus dose vasopressors and mortality. **Key words:** critical care transport; hypotension; epinephrine

PREHOSPITAL EMERGENCY CARE 2019;23:764–771

Introduction

Hypotension in the out-of-hospital environment is common (1). Previous research has linked development of hypotension to dose-dependent increases in mortality in multiple disease states (2, 3). Intravenous (IV) bolus administration of vasopressors is an established treatment for hypotension that has been used for more than a century in the perioperative setting (4, 5). More recently, use of bolus vasopressors has gained popularity in the intensive care unit and emergency department, although data confirming safety and efficacy are lacking (6–8).

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Although any vasopressor can be administered as an IV bolus, phenylephrine, or ephedrine are commonly used perioperatively to counteract vasodilation observed in response to spinal or general anesthesia (9–11).

Undifferentiated shock may be more common in the emergency department (ED) and prehospital environments. Some providers have advocated for low-dose epinephrine administration ("bolus dose epinephrine" [BDE]) out of concern that some forms of shock would benefit from ionotropic support and could be worsened by a pure vasoconstrictor (6, 7, 12–16). BDE may decrease exposure to hypotension and preserve perfusion to the brain and coronary arteries while fluid resuscitation or vasopressor infusions are initiated (6, 7, 12, 13). Despite limited data in the prehospital environment, face validity and a perceived clinical need has led to BDE adoption in many emergency medical services (EMS) systems, including our own. Unfortunately, there is a minimal amount of data supporting the feasibility, safety, optimal dosing, or efficacy of BDE administration in the prehospital setting. Widespread adoption of prehospital BDE limits clinical equipoise necessary for a randomized trial (17).

We tested if BDE administration to profoundly hypotensive patients during critical care transport is associated with survival 24 hours after hospital arrival. Secondary aims included evaluating the association of BDE with survival at hospital discharge and at 30-days. We also examined short-term measures of efficacy including blood pressure response to BDE and the incidence of significant adverse events.

Methods

Setting and Data Sources

We performed a retrospective case-cohort study including patients transported by a single large critical care transport network from January 2011 to January 2017. The University of Pittsburgh Institutional Review Board approved all aspects of this study. We include adult patients ≥14 years of age with profound hypotension, defined as a systolic blood pressure (SBP) <70 mmHg obtained by an automated noninvasive blood pressure cuff, by manual assessment, or by an indwelling arterial catheter. Our regional critical care transport network serves a population of roughly 4 million people from 17 bases with rotor wing and ground critical care assets. The system transports 12,000 patients annually, of which 75% are interfacility transports. Transport teams consist of a board certified critical care paramedic (FP-C) and critical care nurse (CFRN). Care is directed by protocol and by online medical direction from a cadre of 14 EMS physicians.

Care protocols for treatment of hypotension differentiated between distributive, obstructive, hypovolemic, and cardiogenic shock. Depending on shock type, first line treatment for patients with SBP <90 mmHg included administration of IV crystalloid fluid boluses, blood products, or initiation of a continuous vasopressor or inotrope infusion. We introduced BDE during flight crew education sessions in May 2015 and required BDE by protocol in July 2015. We directed crews to administer 100 micrograms epinephrine (1 mL of 0.1 mg/mL epinephrine) through a running wide-open line of 0.9% sodium chloride to patients with preserved pulses and SBP <70 mmHg. The crew had the option to repeat that dose up to 4 times until the blood pressure exceeded 70 mmHg. This bolus dose of epinephrine is 2–10 times higher than typically used in other resuscitative environments and in the local EMS protocols. The protocol directed them to simultaneously initiate resuscitation with a volume bolus (the size of which varied depending on the shock type), followed by a norepinephrine infusion, irrespective of the type of shock suspected. For patients who remained hypotensive after initial volume resuscitation and initiation of a norepinephrine infusion, and for patients who required more than 4 doses of BDE, crews were instructed to consult with a medical command physician. By protocol design, administration of BDE was intended to serve as a temporizing measure until additional resuscitation could be performed.

Flight crews documented prehospital patient data and record vital signs at least every 5 minutes for the duration of patient contact. Charting was completed using a prehospital electronic health record (EHR) (emsCharts, Warrendale, PA). Vital sign data were automatically time stamped. To aggregate these data, we exported SQL files from available EHR data for every transport during the included date range. We then organized this file into a series of data tables including time-invariant patient characteristics, and time varying medication, vital sign, and procedure data for all patients.

Exposures, Covariates and Outcomes

We first identified a cohort of patients potentially eligible for BDE treatment based on the 2015 protocol regardless of the year transported. Included in this cohort was any patient with at least one documented SBP <70 mmHg. We then identified all administrations of BDE, not including administration of higher doses of epinephrine (primarily 1 mg), which administered only in treatment of cardiac arrest. In the cohort of hypotensive patients, we then cross-tabulated year

TABLE 1. Characteristics of patient cohorts pre-index event

	All patients ($n = 3,302$)	No PDE cohort ($n = 2,731$)	PDE cohort ($n = 571$)	P value
Female gender (n, %)				
Male	1,694 (51.3)	1,406 (51.4)	288 (50.4)	
Female	1,587 (48.1)	1,311 (48.0)	276 (48.3)	0.1430
Age in years (mean, SD)	59.7 (18.2)	59.0 (18.2)	62.9 (17.9)	<0.0010
Weight in Kg (mean, SD)	89.4 (30.1)	89.8 (29.9)	87.5 (30.8)	0.0940
Race (n, %)				0.0810
American Indian	2 (0.06)	2 (0.07)	0(0.00)	
Asian/Pacific Islander	7 (0.21)	6 (0.22)	1 (0.18)	
Black	159 (4.82)	133 (4.87)	26 (4.55)	
White Hispanic	18 (0.55)	13 (0.48)	5 (0.88)	
White Non-Hispanic	3,020 (91.4)	2,509 (91.8)	511 (89.4)	
Multiracial	1 (0.03)	1 (0.04)	0 (0.00)	
Other	15 (0.45)	13 (0.48)	2 (0.35)	
Unknown	8 (0.24)	6 (0.22)	2 (0.35)	
Type of shock (n, %)				<0.0010
Post-arrest	474 (14.3)	347 (12.7)	127 (22.2)	
Trauma	1,006 (30.4)	857 (31.3)	149 (26.1)	
Cardiogenic	329 (9.96)	278 (10.1)	51 (8.93)	
Distributive	465 (14.1)	352 (12.8)	113 (19.7)	
Obstructive	121 (3.66)	98 (3.58)	23 (4.03)	
Stroke	125 (3.79)	104 (3.81)	21 (3.68)	
Uncharacterized	782 (23.6)	695 (25.4)	87 (15.2)	
Vital signs prior to index (mean, SD)				
Heart rate (bpm)	98.9 (27.1)	99.2 (26.4)	97.7 (29.6)	0.2327
SBP (mmHg)	95.4 (28.1)	100 (27.1)	74.8 (22.9)	<0.001
DBP (mmHg)	60.2 (21.3)	63.1 (21.2)	47.7 (17.1)	<0.001
Oxygen Saturation (%, CI)	97 [93 – 100]	98 [94 – 100]	96 [91 – 99]	0.001
$EtCO_2$	32.0 (12.1)	32.2 (12.2)	31.3 (11.6)	0.2514
GCS	7 (3–15)	8 (3–15)	3 (3–10)	0.001
Lactate mmol/L (mean, SD)	1.33 (3.08)	1.11 (2.72)	2.41 (4.26)	<0.001
Airway status (n, %)				
Compromised	356 (10.7)	286 (10.4)	70 (12.2)	
Secured/Intubated*	1,696 (51.3)	1,321 (48.3)	375 (65.6)	<0.001
Arterial line (n, %)	243 (7.36)	209 (7.65)	34 (5.95)	0.157
CPR performed (n, %)	99 (3.00)	67 (2.45)	32 (5.60)	<0.001
Defibrillation performed (n, %)	29 (0.88)	24 (0.88)	5 (0.88)	0.994
Pacing performed (n, %)	50 (1.51)	41(1.50)	9 (1.58)	0.894
Needle decompression (n, %)	34 (1.03)	24 (0.88)	10 (1.75)	0.060
Intubation performed (n, %)	347 (10.5)	285 (10.4)	62 (10.8)	0.765
Vasopressor dependent (n, %)*	715 (21.6)	512 (18.7)	203 (35.5)	<0.001

SBP = *systolic blood pressure*; DBP = *diastolic blood pressure*; $EtCO_2$ = *end tidal* CO_2: GCS = Glasgow Coma Scale score. *Characteristics prior to flight crew arrival.

(pre- or post-2015) with BDE administration, and calculated the BDE-treated patients in each epoch. We believed patients treated off-protocol would differ systematically from those treated on-protocol. Thus, for our primary analysis, we excluded any patient treated off-protocol (i.e., patient treated with BDE before the 2015 protocol change or those untreated after the protocol change). We performed statistical matching (see the following paragraph) only on the subset of subjects treated on protocol. For analyses of short-term physiological BDE effects, we included all eligible patients. For analyses of survival to hospital admission, hospital discharge, 30-day survival, we included only those patients transported to one of 5 regional referral centers for which we had access to in-hospital data.

Additionally, from the full Structured Query Language (SQL) database, we extracted each patient's age, gender, race, ethnicity, time-stamped vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, oxygen saturation, end-tidal carbon dioxide, and Glasgow Coma Scale score), airway status (patent, compromised, endotracheally intubated), cardiac rhythm, venous lactate, key procedures (cardiopulmonary resuscitation, defibrillation, transcutaneous pacing, new endotracheal intubation, needle thoracostomy), key medications (fluid and continuous vasopressor infusions); and EMS process variables (response time, scene time, and transport time). For time dependent variables, we divided each patient encounter into 2 epochs: before the index hypotensive event and after the index hypotensive event. We summarized these

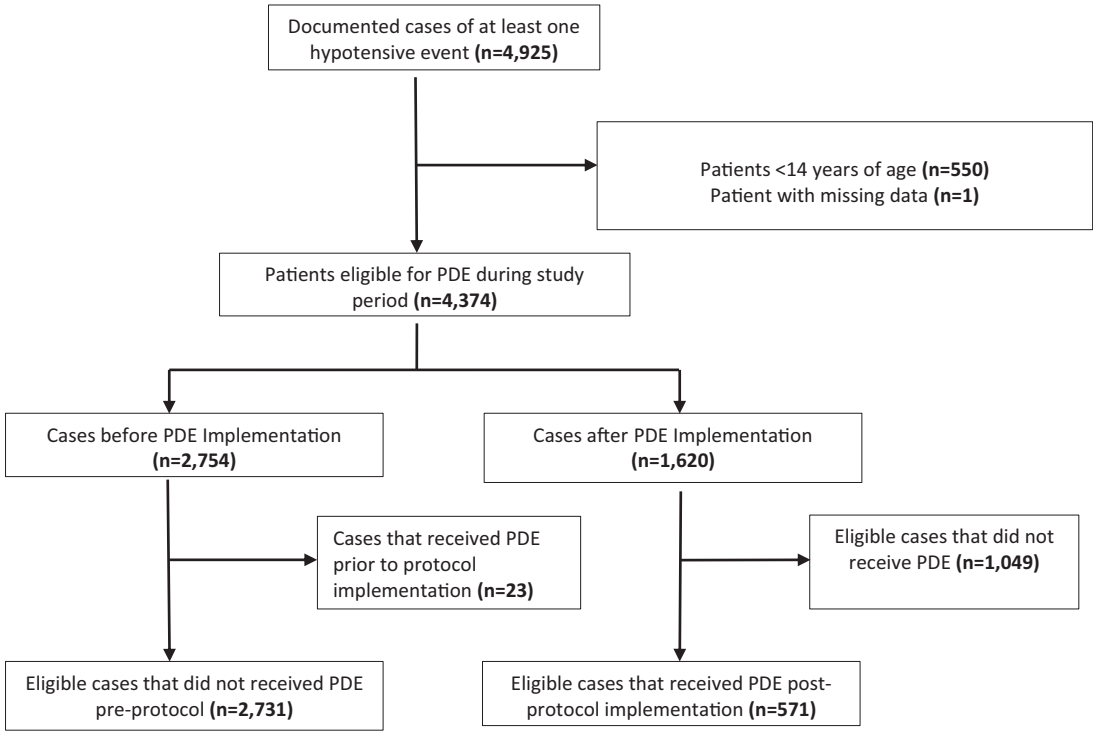

Figure 1. Consort diagram of patients eligible for bolus dose epinephrine (BDE).

time dependent variables in both of these epochs for each. Finally, we searched each patient's free-text history of present illness, chief complaint, and provider impression to adjudicate what cause of shock was suspected by the treating providers.

To obtain our primary outcomes of interest, we generated an identifiable dataset with each patient's name, date of birth, gender, date of service and medical record number, and then used these identifiers to extract data from our in-hospital electronic health record (Cerner, Kansas City, MO). We limited data collection to patients transported to one of the hospitals in our health network. Specifically, we extracted 24-hour survival, survival to hospital discharge, and 30-day survival. To minimize the potential for survival bias, we included EMS-treated patients that died in the field and were never transported in all analyses. We considered these subjects to have not survived to admission, discharge or 30 days. We assigned their receiving hospital (i.e., would the patient have been transported to an included hospital) based on data retrieved from the service's dispatch operations software (Flight Vector, Softtech, Henderson, NV).

Our secondary outcomes were abnormal vital signs within 10 minutes of the index event (persistent hypotension <70 mmHg, severe hypertension >220 mmHg), tachydysrrhythmia (ventricular tachycardia, ventricular fibrillation or cardioversion/defibrillation administered), need for cardiopulmonary resuscitation; and new post-treatment infusion vasopressor administration.

Statistical Methods

We summarized overall population characteristics using descriptive statistics and report raw numbers with corresponding percentages, means with standard deviation, or medians with interquartile range as appropriate. We calculated the percentage of patients with hypotension treated on protocol before and after 2015. We used *t*-tests and X^2 tests to compare overall cohort characteristics of the historical controls with BDE-treated patients and summarized these results. To account for multiple between-cohort differences in these characteristics, we used nearest neighbor matching on multiple parameters to estimate the average treatment effect for BDE administration at the population level. In these models, we adjusted for age, gender, shock type, weight, type of service, index vital signs at the time of the first hypotensive episode, and pretreatment characteristics including cardiopulmonary resuscitation, defibrillation, transcutaneous pacing, needle thoracostomy, vasopressor administration, intubation or arrhythmia (Table 1). We matched each BDE case to 2 historical controls and considered a P value of <0.05 from the treatment-effects estimation to be significant. We used Stata Version 14.2 (StataCorp, College Station, TX) for all analyses.

To assess for residual bias after matching, we selected a random subset of 60 match cases and controls. We redacted these EMS charts, removing all

TABLE 2. Characteristics and patient outcomes following the index event

Events during transport	All patients ($n = 3,302$)	No PDE cohort ($n = 2,731$)	PDE cohort ($n = 571$)	P value
Mean (CI) SBP (mmHg) 10 minutes after index event	90.7 (89.6–91.7)	88.9 (87.8–90.0)	98.9 (96.1–101)	<0.001
SBP < 70 within 10 min of the index event	1,068 (32.3%)	880 (32.2%)	188 (32.9%)	0.744
SBP < 70 any time after the index event	1,741 (52.7%)	1,350 (49.4%)	391 (68.4%)	<0.001
SBP >220 any time after index event	42 (1.27%)	27 (0.99%)	15 (2.63%)	0.001
SBP >220 within 10 min of the index event	9 (0.27%)	5 (0.18%)	4 (0.70%)	0.031
Rhythm after index event				
Perfusing	2,905 (87.9%)	2,540 (93.0%)	365 (63.9%)	0.001
Shockable	46 (1.39%)	43 (1.57%)	3 (0.53%)	
Non-shockable	49 (1.48%)	47 (1.72%)	2 (0.35%)	
CPR after index event	268 (8.12%)	181 (6.63%)	87 (15.2%)	<0.001
Defibrillation after index event	66 (2.00%)	46 (1.68%)	20 (3.50%)	0.005
Vasopressors after index event	1,213 (36.7%)	841 (30.7%)	372 (65.1%)	<0.001
Hospital outcomes	$n = 1,439$	$n = 1,244$	$n = 195$	P value
24 hour survival	1,149 (79.8%)	1,023 (82.2%)	126 (64.6%)	<0.001
Survival to discharge	826 (57.4%)	743 (59.7%)	83 (42.5%)	<0.001
30 days survival	775 (53.8%)	701 (56.3%)	74 (37.9%)	<0.001
Length of Stay (LOS) (days: median (IQR))				
Hospital LOS overall	6 (2–14)	6 (2–15)	3 (1–11)	<0.001
Hospital LOS: if survival to discharge	10 (5–20)	10 (5–19)	12 (8–22)	0.026
ICU LOS	3 (1–8)	3 (1–8)	2 (1–7)	0.024
ICU LOS: If survival to discharge	5 (2–12)	4 (2–11)	7 (3–14)	0.001

SBP = systolic blood pressure.

documentation of BDE administration or several non-BDE treatments in the case of controls (e.g., a dose titration of vasopressor). We asked 2 blinded physicians with EMS experience to rate the severity of illness for each patient on a 10-point Likert scale. We also assessed the adequacy of redaction by asking the physicians to judge if each chart represented a case or control. We averaged the 2 raters' illness severity measures and compared cases and controls using a Wilcoxon rank-sum test.

RESULTS

Overall, we identified 6,992 patients treated by STAT MedEvac who had at least one documented SBP <70 mmHg. Of these, we excluded 550 for age <14 years and 1 missing data. We also excluded 2,067 who were treated before January 1′ 2011. Of the remaining 4,374 patients, 2,754 were transported before BDE protocol implementation and 1,620 were transported after protocol implementation. In the pre-protocol period, 23 patients (1%) received BDE while after protocol implementation 571 (35% of eligible patients) received BDE. Thus, we eliminated 1,072 patients not treated per protocol and included 3,302 in our analyses of prehospital endpoints. Of these patients treated per protocol, 1,438 (43%) were transported to one of the 5 hospitals for which we had access to in-patient data and thus included in our analyses of post-transport survival. Of these, 197 received BDE (Figure 1).

Of BDE-treated patients, 229 (38%) received a single dose, 156 (26%) received 2 doses, and the remainder received 3 or more doses. There were multiple baseline differences between the 2 cohorts of patients treated per protocol (Table 1). All of these were adjusted for by nearest neighbor matching procedures. Overall, a total of 1,149 patients (80%) survived 24 hours after hospital arrival, with a significantly lower survival rate among BDE-treated patients (127 of 195 (65%) vs. 1,022 of 1,243 (82%), $P < 0.001$). In adjusted analysis, 24-hour survival remained lower in BDE-treated patients (ATE coefficient −0.150, 95% confidence interval (CI) −0.244 to −0.055, $P = 0.002$). Overall survival to discharge was 57%, and was also lower in BDE-treated patients without adjustment (43% vs. 60%, $P < 0.001$), but was no longer significant after adjustment (ATE coefficient −0.113, 95%CI −0.228 to 0.002, $P = 0.05$). Overall, 30-day survival was 54%, and was lower in BDE-treated patients both without adjustment (38% vs. 56%, $P < 0.001$) and with adjustment (ATE coefficient −0.145, 95% CI −0.256 to −0.033, $P = 0.01$) (Table 2).

Our analyses of prehospital safety and efficacy outcomes included all 3,304 patients that were treated with the intent to transport. In the 10 minutes after the index hypotensive event, mean blood pressure was significantly higher among BDE-treated patients than historical controls (99 mmHg vs. 89 mmHg, $P < 0.0001$) and remained significant after nearest neighbor matching (ATE coefficient 13.7, 95% CI 8.0 to 19.4, $P < 0.001$). There was no difference in the incidence of SBP <

TABLE 3. Adjusted outcomes following nearest neighbor match

Events during transport	*N*	ß coefficient*	95% CI	*P* > |z|
Mean SBP 10 minutes after index event (mmHg)	2,647	12	6.3–17.6	0.000
SBP <70 within 10 min of the index event	2,884	−0.01	−0.08 to 0.06	0.830
SBP <70 any time after the index event	2,884	0.01	−0.05 to 0.07	0.864
SBP >220 any time after index event	2,884	0.01	−0.01 to 0.02	0.332
SBP >220 within 10 min of the index event	2,884	0.01	−0.01 to 0.02	0.340
CPR after index event	2,884	0.07	0.02–0.12	0.003
Defibrillation after index event	2,884	−0.00	−0.01 to 0.01	0.354
Vasopressors after index event	2,884	0.32	0.25–0.39	0.000
Hospital outcomes	**N**	**ß coefficient***	**95% CI**	**P>|z|**
24 hour survival	1,380	−0.15	−0.24 to (−0.05)	0.002
Survival to discharge	1,380	−0.11	−0.22 to 0.00	0.053
30 days survival	1,380	−0.14	−0.25 to (−0.03)	0.012
Hospital LOS	793	4.48	−1.03 to 10.0	0.111
ICU LOS	792	1.92	−0.26 to 4.09	0.085

SBP = systolic blood pressure; BDE = bolus dose epinephrine.

*A beta coefficient less than 0 with a 95% confidence interval that does not cross zero suggests a significant negative association between the predictor of interest (in this case, BDE) and the outcome being reported. The absolute value of the coefficient reflects the magnitude of the effect.

70 mmHg within 10 minutes of treatment between cases and controls either in unadjusted analysis (33% vs. 33%, P = 0.98), or after adjustment (P = 0.42). However, over the entire duration of treatment after the index event, a significantly higher proportion of BDE-treated patients had recurrent hypotension with SBP <70 mmHg at least once more (68% vs. 50%, P < 0.001), a difference that persisted after adjustment (ATE coefficient 0.09, 95%CI 0.05 to 0.16, P = 0.02). There was a significant increase in the incidence of SBP >220 mmHg within 10 minutes of the index hypotensive episode among BDE-treated patients (1% vs. 0%, P = 0.03), a difference that did not persist after adjustment (P = 0.35). As expected by protocol design, significantly more BDE treated patients received a vasopressor infusion after the index hypotensive event (65% vs. 31%, P < 0.001). Significantly more BDE-treated patients required CPR at some point after the index hypotensive event (15% vs. 7%, P < 0.001), a difference that persisted after adjustment (ATE coefficient 0.073, 95%CI 0.023 to 0.123, P = 0.004). The proportion of patients requiring defibrillation after the index hypotensive event was also greater in unadjusted analysis (3% vs. 2%, P = 0.005), but this was not significant after adjustment (P = 0.69) (Table 3).

In our assessment for residual bias on blinded chart review, BDE cases were not significantly sicker on a 10-point Likert scale (rank sum P = 0.053). However, redaction was only moderately effective, with reviewers correctly identifying whether charts came from cases or controls for 69% of cases (P for test of proportions vs. 50% = 0.005).

DISCUSSION

The use of BDE in the treatment of patients with profound prehospital hypotension results in improvements in blood pressure and allows sufficient time to initiate resuscitative measures with vasopressors and volume resuscitation. The administration of BDE is intended to mitigate the exposure of the patient to secondary injury caused by hypotension. This hypotension may occur during the initial resuscitation, or as the result of interventions associated with further exposure to hypotension including intubation and positive pressure ventilation (18). In addition, it may be necessary to temporize regarding a patient who has had a sudden change in perfusion secondary to uncontrolled hemorrhage, outflow obstruction, tamponade, or tension pneumothorax. While not curative, BDE may allow for recognition, diagnosis, and definitive treatment of the condition.

Our analysis identified that patients who received BDE after protocol implementation had worse outcomes than similarly eligible patients before protocol implementation. This would suggest an intervention that adversely impacts patient care. However, our further analysis of cases demonstrated that in spite of robust adjustment for potential confounders, the subset of post-protocol patients who received BDE were likely sicker than eligible patients matched before protocol implementation. For example, a greater proportion of BDE-treated patients had recurrent hypotension, received a vasopressor infusion, or required CPR at some point, even after robust adjustment for potential confounders. These findings highlight the challenge of drawing causal conclusions from a retrospective analysis and suggest the need for a randomized controlled trial of BDE.

The ideal bolus dose vasopressor may be patient dependent, and equipoise exists with respect to indication, agent, and dose. The indication for bolus dose vasopressors depends on the minimum perfusion needed for the patient. The appropriate trigger

and endpoint for this therapy is unknown and may vary widely based on the physiology. The young trauma patient, for example, may benefit from permissive hypotension, and needs only to have enough perfusion to prevent cardiac arrest (19). The addition of BDE may result in increased bleeding through clot disruption and more rapid exsanguination given increased blood flow to injured tissues. Perhaps a pure vasoconstrictor would decrease blood loss while increasing preload long enough to support perfusing vital tissue during hemorrhage control and volume replacement. The value of vasopressors versus permissive hypotension in hypovolemic shock may also differ in young previously healthy individuals subject to sudden hemorrhagic shock, compared to older patients with baseline hypertension or trauma patients with concomitant traumatic brain injury. Similarly, patients in cardiogenic shock may require greater diastolic pressures for coronary perfusion in order to prevent further ischemia or arrest. These patients may require increased inotropy while minimizing increased myocardial oxygen consumption and afterload. With respect to dose, few data exist as to the appropriate dose of a bolus dose vasopressor. Bolus doses of intravenous epinephrine have varied widely by indication ranging from doses as high as 1 mg in arrest or anaphylaxis to 5–10 mcg for the treatment of transient hypotension related to anesthesia (5, 8, 20). The doses of epinephrine (10–20 mcg) most commonly in use for immediate blood pressure control are derived from anesthesia literature (16). We chose a larger dose, 100 mcg, for 2 reasons. First, the patient population we selected for this intervention had profound hypotension (SBP $<$ 70) and was either peri-arrest or had failed initial resuscitation measures. Second, we sought to minimize delay and dosing errors through the use of a small aliquot from a prefilled epinephrine (0.1 mg/mL) syringe. The higher dose of epinephrine may be associated with deleterious effects including decreased end organ perfusion, increased myocardial oxygen consumption, or increased risk of ectopy. There is no dose response curve in the clinical literature and it may be reasonable to assume that future studies employ the lowest effective dose.

This study indicates that BDE is not associated with immediate adverse events including cardiac arrhythmia, profound tachycardia, or severe hypertension. Despite these findings, BDE is associated with an increased need for CPR and a higher incidence of mortality. This may be the result of uncontrolled bias and raises the ultimate need for a definitive trial. Alternatively, BDE may worsen survival through detrimental physiologic effects, subsequent end organ injury, or worsening the patient's baseline condition which resulted in the index hypotensive event. As previously noted, BDE could worsen cardiogenic shock through worsening ischemia or depressed cardiac output and hemorrhage through clot disruption. Paur et al. have suggested that high circulating levels of epinephrine could result in Takotsubo such as cardiodepression (21). Despite improvement in blood pressure and perfusion within 10 minutes of administration, the administration of BDE is not associated with increased survival. It is however associated with an increase in the need for post administration CPR and increased vasopressor dependence. Given the limitations of this study, we cannot determine if these findings are the result of inherent differences in the patient population or are a consequence of treatment with BDE. These questions can only be answered with an interventional trial.

LIMITATIONS

This retrospective study is subject to a variety of biases which could not be controlled for despite the use of robust methods adjusting for known confounders. As with any prehospital data there may be recall bias or errors in reporting of data and events. Among the biases which may have contributed to the findings, indication bias was likely present as most patients with index systolic blood pressures $<$70 mmHg did not receive BDE, perhaps because these values were false readings, transient, or reversed by other means (fluids, blood, or vasopressors). Selection bias likely occurred as providers only administered BDE to 36% of patients with eligible vital signs. Perhaps the care teams recognized a sicker cohort of patients through clinical gestalt and limited BDE administration to that group of patients. Although the protocols are not optional we do have deviations. They can occur because of spontaneous resolution of the hypotension, resolution through other means listed in the protocol (fluids, blood products, titration of vasopressor infusions), alternative interventions suggested by during a physician consult (62% of patients require a physician consult) or because of human error (misapplication of the protocol or failure to recognize an actionable vital sign). Despite our attempts to control for it, a survival bias may be present, manifesting as patients who lived to hospital arrival but did not survive to hospital admission or through the first 24 hrs. We matched cohorts in this study using available prehospital data but had limited inpatient data precluding the use of calculated risk scores (ISS, SOFA, SAPS-2) in the matching process.

Following nearest neighbor matching, our cohorts differed significantly in SBP, diastolic blood pressure (DBP) and lactate levels. These differences were statistically significant but are unlikely to be clinically significant as they amounted to differences of 2 mmHg for both systolic and diastolic blood pressure and 0.4 mmol/L of lactate. Our data also indicate that patients being transported in our system are increasingly more complex, with the proportion requiring vasopressors and mechanical ventilation increasing over the time period of the study. This and other secular trends could have influenced the observations in this study.

Conclusion

Bolus dose epinephrine when administered during profound prehospital hypotension increases blood pressure. Bolus dose epinephrine decreases hypotension dose and may create a window of opportunity to initiate other resuscitative measures. Despite robust measures to control for confounding, BDE remained associated with increased mortality in this observational cohort. Further study is necessary to determine the optimal indication, dose and agent for use as a prehospital bolus dose vasopressor and a randomized trial may be necessary to provide a definitive answer.

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