Choosing a Vasopressor for a Prehospital Emergency Medical System: Consideration for Agent Selection and Review of Pharmacologic Profiles, Efficacy, and Safety in Treatment of Shock

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ABSTRACT

Introduction: Prehospital medical teams encounter patients with varying states of shock that require the use of vasopressors for hemodynamic support during transport. Selection of a vasopressor is challenging due to the absent comparative literature in prehospital medicine, as well as practical limitation of use in an ambulance.

Areas Covered: This article discusses specific challenges in the delivery of vasopressor support for hemodynamically compromised patients in the prehospital environment. Discussion includes the current state of vasopressor use in prehospital medicine, use of a patient-specific agent selection or "one-vasopressor-fits-all" modality, as well as considerations for each vasopressor based on practical, pharmacologic, and comparative evidence-based evaluations.

Conclusions: There are currently many limitations to assessment of shock etiology in the prehospital setting. A "one-vasopressor-fits-all" strategy may be most feasible for most prehospital emergency medical services (EMS) systems. No clear difference in extravasation exists amongst agents. Based on current evidence, norepinephrine may be more efficacious and have a better safety profile than other vasopressors in cardiogenic, distributive, and neurogenic shocks. Due to its suitability for most shocks, norepinephrine is a reasonable agent for EMS systems to employ as a "one-size-fits-all" vasopressor.

BACKGROUND

Shock is one of many conditions encountered by Emergency Medical Services (EMS) and is defined by the dysfunction of oxygen delivery from a state of circulatory failure. Circulatory support with vasoactive medications plays a vital role in treatment of shock.

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While prehospital providers often encounter varying states of shock, vasopressors are utilized infrequently.[1,2] A possible contributor to this infrequent use may be the challenges created in selecting the appropriate prehospital agent given the wide array of vasoactive agents and shock etiologies. According to data from the National EMS Information System (NEMSIS), dopamine was the most commonly used prehospital vasopressor in the United States in 2017.[3] However, other countries like France show norepinephrine as the predominantly used agent.[4]

In addition to safety and efficacy, there are many factors to consider when choosing a vasopressor for a prehospital formulary. Lack of invasive monitoring capabilities, difficult conditions for drug preparation, shelf life of unused drugs, and potential harms associated with unmonitored or peripherally administered medications all play a role in agent selection. The purpose of this article is to discuss specific challenges in the delivery of protocol-based vasopressor support for hemodynamically compromised patients in the prehospital environment. The article will provide considerations for agent selection based on practical, pharmacologic, and evidence-based evaluations.

ADMINISTRATION METHOD: BOLUS VASOPRESSORS OR INFUSION

Bolus- or "push-dose" vasopressors refer to the use of syringes with phenylephrine, epinephrine, or ephedrine given in intermittent boluses for the management of hypotension. Two studies and 1 case series exist describing the use of prehospital bolus-dose vasopressors.[5-7] One study reported efficacy and safety

after 100 administrations of push-dose epinephrine (10 mcg per dose) during the critical care transport of patients after return of spontaneous circulation (ROSC) (n = 24), in septic (n = 9) or cardiogenic shock (n = 3), or other patients (n = 7). The rate of dosing errors was 6.0%, and rate of effective hypotension resolution after correctly dosed bolus was 58.5%. No significant patient harm occurred from use; however, 1 patient experienced an extreme episode of transient hypertension after bolus administration.[5] Another large retrospective case-control study evaluated the effect of 100 mcg epinephrine boluses for up to 4 doses for hypotension. Of 571 patients, 62% required additional dosing after a single bolus. While blood pressure remained elevated compared to matched controls, the bolus-dose epinephrine group had more episodes of hypertension > 220 mmHg, recurrent hypotension, and cardiac arrest after administration. Patients treated with epinephrine required a vasopressor infusion in 65% of cases. No safety events or dose errors were reported among the 571 patients.[6] One case series also describes the use of bolus-dose vasopressors in the peri-intubation period for 2 patients. No adverse effects occurred in the patients who received these doses.[7]

The majority of data regarding use of these push-dose vasopressor agents are derived from anesthesia data that use precompounded products in the controlled environment of the operating room.[8] There is a paucity of data within the emergency department (ED) setting where these agents are used for peri-intubation hypotension, medication-related hypotension, or as a bridge to a long-term vasopressor.[8-12] Recurrence of hypotension is more likely with bolus doses of vasopressors compared to infusions given the short duration of action, which often necessitate additional vasopressor as demonstrated by up to 65% of patients requiring infusions after a bolus dose.[6,9,11] Furthermore, complex dilutions often are needed to prepare these medications, which may lead to higher rates of error.[10,12]

Given the concern for compounding error and data supporting frequent vasopressor infusions after bolus doses, the infusion strategy may be a more definitive option in the prehospital setting. However, there is a lack of comparative safety and efficacy data with bolus dosing compared to infusion. More evaluation is needed to determine the role of push-dose vasopressors in the prehospital setting. Safety considerations and guidelines for safe use of bolus-dose vasopressors in the ED were published recently.[10]

EXTRAVASATION RISK

Data comparing vasopressors for their relative risk of extravasation are lacking, and rates of prehospital extravasation of vasopressors have not been studied. Vasopressors carry varying ratios of vasodilatory β and vasoconstrictive α adrenoreceptor effect. There are theoretical advantages for agents with more vasodilatory β2 effect than α1 effect, as they may cause less vasoconstriction in the setting of extravasation. However, no clinical data are evident to support this.

Studies evaluating complication rates of peripherally run vasopressors (primarily phenylephrine or norepinephrine) cite complication rates between 2.0% and 5.5%.[13-18] If vasopressor extravasation occurs, catheter site placement, duration of infusion, drug concentration, and volume of drug contribute to the degree of tissue injury from extravasation.[14] Local tissue injury events occur more often with peripheral infusions of more than 4 hours in catheters placed distal to the antecubital or popliteal fossae.[15]

As prehospital teams continue to transport critically ill patients, the need for prehospital vasopressors is unlikely to diminish. No data support a stronger safety profile for any single agent. Further study is needed to evaluate the risk of extravasation by vasoactive agent and site of administration in the prehospital setting. Additionally, study of the clinical impact of prehospital extravasation, such as rate of injury or impact on clinical outcomes, is warranted.

CHALLENGES IN PREHOSPITAL AGENT SELECTION

Shock is manifested by a dysfunction in one or more components of the cardiovascular system, cardiac preload, afterload, or cardiac output. Based on the underlying deficit and subsequent compensatory changes in afterload, preload, or cardiac output, shock can be characterized into 3 primary phenotypes: cardiogenic (and cardiogenic obstructive), distributive (and neurogenic distributive), and hypovolemic. Treatment for each shock state is based on correcting the underlying hemodynamic derangement that caused the compensatory changes.[18] Table 1 summarizes shock phenotypes and guideline-recommended treatments.

Each vasopressor has a unique effect on cardiac output and afterload. Selection of an agent tailored to an individual's hemodynamic profile may maximize benefit while limiting harmful side effects.[19] In contrast to an ED or intensive care unit (ICU) setting, prehospital transport teams often lack tools like ultrasound, arterial lines, or pulmonary artery catheters that aid in identifying the specific hemodynamic derangement. This severely limits the ability to tailor vasopressor selection. Misdiagnosis and possible undue harm may come to a patient who receives an inappropriate vasopressor for their shock state.

AGENT SELECTION STRATEGY: ONE VASOPRESSOR FITS ALL

One strategy for agent selection would be to choose an agent that meets the needs of the most frequently encountered causes of prehospital shock. The most commonly coded scenario in the NEMSIS database in 2017 that required vasopressor administration was cardiac arrest, respiratory arrest, or cardiac rhythm disturbance (1212 documented occurrences) followed by hypovolemia and shock (428 occurrences).[3] Traditionally, vasopressors have a very limited role in hypovolemic shock and may increase mortality

Table 1. Shock Phenotypes and Guideline Recommended Treatment

Shock subtype	P	CO	SVR	Guideline recommended treatments
Septic[23] (Distributive)	↓	↔ Or ↑	↓	Surviving sepsis campaign recommendations • 30 ml/kg crystalloid fluid (preload correction) • Norepinephrine 1st line (afterload correction) • Vasopressin OR epinephrine 2nd line • Dopamine only in bradycardia with low risk of arrhythmia • Dobutamine if persistent hypotension despite adequate fluid
Hypovolemic	↓	↓	↑	Hemorrhagic[21] • Replacement of lost blood volume, minimal roll of vasoactive agents Dehydration • Replacement of lost fluids
Neurogenic[42]	↔	↓	↓	Consider vasopressor agents with both α- and b-adrenergic activity if high cervical/thoracic injury
Cardiogenic shock[25]	↑	↓	↑ or ↔	Abbreviated American Heart Association recommendations • Norepinephrine is associated with fewer arrhythmias and may be the vasopressor of choice in many CS patients. ***Recommendations by phenotype:*** Classic wet and cold (Low CO, high preload, high SVR), or euvolemic cold and dry (Low CO, normal preload, high SVR) • NE if high HR or pro-arrhythmic, DA if low HR however, arrhythmia risk higher, inotropic agent when stabilized and after revascularization (MI only) Vasodilatory warm and wet or mixed cardiogenic and vasodilator (low CO, low SVR) • Norepinephrine and invasive hemodynamics-guided therapy

Abbreviations: CI, cardiac index; CO, cardiac output; CS, cardiogenic shock; DA, dopamine; HR, heart rate; MI, myocardial infarction; NE, norepinephrine; P, preload; SVR, systemic vascular resistance (afterload).

in hemorrhagic shock, as volume expansion through blood products or intravenous (IV) fluids is the preferred treatment modality.[19-21] Post cardiac arrest patients with ROSC—the most common indication for need of vasopressors—provides a cornerstone for prehospital therapy selection.

Cardiogenic shock may be present in ROSC patients due to both post cardiac arrest myocardial dysfunction and interventions performed, such as defibrillation.[22] Additionally, etiologies of cardiac arrest cause cardiogenic shock states such as pulmonary embolus, myocardial infarction, or cardiac tamponade. Utilizing a vasopressor that is highly functional in cardiogenic shock would be ideal in a prehospital setting. One that is effective in distributive shock present in patients with sepsis, anaphylaxis, or post cardiac arrest reperfusion injury would be optimal to address most prehospital patients who need pressor support.

Numerous society guidelines recommend specific vasopressors for cardiogenic and distributive shock.[23-25] Additionally, many studies of patients in EDs and critical care units have evaluated comparative hemodynamic effects of vasopressors and clinical outcomes based on the specific shock subsets. Though the available data may have diminished application during shorter EMS transport times, safety and efficacy outcomes in these patient populations should be considered when selecting an agent for prehospital use.

VASOPRESSOR CONSIDERATIONS

To critically evaluate the benefits and challenges of vasopressor agent use in the prehospital setting, below is a review of the pharmacology, safety, efficacy, and practical considerations pertaining to individual medications. As there is little role for vasopressors in hypovolemic shock, discussion will focus on efficacy in cardiogenic and distributive forms of shock.

Narrative Evidence Review Search Strategy and Selection Criteria

Two authors (RF and MS) individually conducted a literature search to assess articles for inclusion. PubMed and MEDLINE were searched with the terms "vasopressor" or "norepinephrine" or "phenylephrine" or "epinephrine" or "dopamine" and "shock" and "prehospital." Abstracts were reviewed for relevance of inclusion. A manual review of reference lists from identified articles also was conducted. English language retrospective or prospective human trials comparing 2 vasopressors in adult patients were included. The search resulted in 36 individual articles; none met criteria for inclusion.

The same search was then carried out with removal of the term "prehospital." Literature reviewed were adult English language retrospective or prospective human trials comparing 1 vasopressor against historical controls or 2 or more vasopressors in adults within cardiogenic, distributive, or neurogenic shock states. Outcomes of interest included rates of mortality, refractory shock, arrhythmia, specific significant differences in hemodynamic parameters, and metabolic abnormalities. Four hundred sixty-four individual articles were identified, of which 29 met inclusion criteria, including 19 prospective randomized interventional or crossover trials, 2 prospective observational cohort studies, and 8 retrospective reviews. Table 2 includes a summary of findings comparing and contrasting data.

Comparative Hemodynamic and Pharmacologic Effects

Each vasopressor has differing effects of β1, β2, and α1, which have varying effects on cardiac output and systemic vascular resistance. Drugs with a predominance for β1 (epinephrine, dopamine) lead to increased heart rate (chronotropy) and stroke volume (inotropy), causing increased cardiac output. Drugs with a predominance for α1 (norepinephrine, phenylephrine) stimulation increase systemic vascular resistance more so than cardiac output. Table 3 provides a summary of the hemodynamic effects of each agent.

Norepinephrine: Stimulates β1, β2, and α1 receptors with a

Table 2. Vasopressor Pharmacologic Profile and Comparative Outcomes

Agent	Hemodynamics CO (β1)	Hemodynamics SVR (α1)	Pro	Con
Norepinephrine	+	+++	• 1st line in septic and cardiogenic shock due to large evidence base supporting safety and efficacy[23,25]	• Less HR and CI increase compared to DA or EP[15,27,28,30,34]
Dopamine	+++	++	• Increases HR if bradycardic, increases CO more than NE[27,29] • Long shelf life	• Concern for increased mortality in cardiogenic shock[44] • More arrhythmogenic than NE[50,51] • May be less effective than NE in septic shock[44,45]
Epinephrine	+++	+++	• Increases HR if bradycardic, increases CO more than NE or DA[28,30,34] • 1st line in anaphylaxis[37] • 2nd line recommendation in septic shock[23]	• Possible increase in mortality or refractory shock in cardiogenic shock and prehospital transport[6,33,54] • Increased lactate production may confound resuscitation[31,32,35,36,46]
Phenylephrine	-	+++		• May decrease cardiac output through reflex bradycardia or reduced stroke volume[38,52] • Limited utility in undifferentiated shock

Abbreviations: CO, cardiac output; DA, dopamine; EP, epinephrine; HR, heart rate; NE, norepinephrine; SVR, systemic vascular resistance.

higher affinity for α1 than β. Smalls studies have shown the primary vasoactive effects of norepinephrine to be through an increase in systemic vascular resistance while maintaining cardiac output.[26] Compared to dopamine, norepinephrine maintains mean arterial pressure without as large of an increase in cardiac index or myocardial oxygen demand.[27-30] It causes significantly less cardiac output increase compared to epinephrine.[31,32]

Dopamine: Stimulates dopamine receptors and the adrenergic receptors β1, β2, and α1 with a predominant effect on β1. The resultant increase in mean arterial pressure is primarily through an increase in cardiac output, as opposed to increasing systemic vascular resistance.[26-29] It has a greater effect on cardiac output than norepinephrine, though it appears to be less than that of epinephrine.[27,29]

Epinephrine: Stimulates β1, β2, and α1 receptors. In comparison to norepinephrine, it has greater affinity for β1 and β2 stimulation, leading to a larger increase in cardiac output with similar increase in systemic vascular resistance. It also increases lactate production and may be associated with a lower pH and more metabolic derangement than norepinephrine during resuscitation.[31-36] Its affinity for β2 stimulation may be of benefit in anaphylactic conditions due to increased bronchiolar dilation.[37]

Phenylephrine: Stimulates only α1 receptors, increasing mean arterial pressure through an increase in systemic vascular resistance. In patients with myocardial dysfunction, it has been shown to increase systemic vascular resistance and reduce cardiac output and stroke volume,[38] giving this agent the potential to worsen cardiogenic shock.

Guideline Recommendations for Vasopressor Use

Norepinephrine: Carries a recommendation as a preferred vasopressor in cardiogenic shock under multiple guidelines and is the first-line recommended agent for septic distributive shock.[23,25,39-41]

Dopamine: Carries low levels of evidence recommendation as an alternative to norepinephrine in septic shock only in those with bradycardia and low risk of arrythmia. It carries recommendations to avoid use in ischemic cardiogenic and neurogenic shock.[23-25,39,41,42] It is also recommended as a possible agent in cardiogenic shock with a low heart rate, with the caveat that it may be more arrhythmogenic (Table 2).

Epinephrine: There are no recommendations listed in societal guidelines for or against the use of epinephrine in the management of cardiogenic shock. Epinephrine is recommended as a preferred agent for anaphylactic shock due to theoretical increased β2 dilation of airways and possible immunomodulation of mast cells.[37] It is recommended as a second-line agent after norepinephrine in the treatment of sepsis.[23]

Phenylephrine: Recommended for consideration in initial vasoactive management of cardiogenic shock due to aortic stenosis, mitral stenosis, or dynamic left ventricular outflow tract (LVOT) obstruction due to theoretical disease-specific advantages rather than clinical data.[24] Although previously recommended for use in 2012 surviving sepsis guidelines in the setting of cardiac dysrhythmias or refractory shock, current sepsis guidelines make no recommendation on phenylephrine use.[23,43] Avoidance of phenylephrine is suggested in the setting of spinal cord injury shock with higher spinal column injuries.[42]

Narrative Literature Review of Efficacy and Safety

A brief summary of comparative efficacy trials identified during literature review are provided below. Table 3 contains key points regarding hemodynamic effects, safety, and efficacy extracted from these trials.

Cardiogenic Shock

Norepinephrine vs Dopamine: A large prospective trial of ICU

patients requiring vasopressors (N = 1679) compared dopamine to norepinephrine. In the subgroup analysis of cardiogenic shock patients, dopamine (n = 135) had greater 28-day mortality than norepinephrine (n = 145) (incidence not reported, $P = 0.03$).[44]

Norepinephrine vs Epinephrine: A randomized trial compared norepinephrine (n = 30) to epinephrine (n = 27) in patients with ischemic cardiogenic shock. Norepinephrine had significantly lower rates of refractory shock (37.0% vs 7.0%, $P = 0.008$) and a lower composite outcome of 7-day mortality or need for extracorporeal life support (37.0% vs 13.0%, $P = 0.045$) compared to epinephrine.[33]

Phenylephrine: No comparative data exist evaluating phenylephrine in cardiogenic shock. One prospective case series of phenylephrine administration in patients with heart disease demonstrated a further reduction in cardiac output when phenylephrine was administered.[38]

Summary: In cardiogenic shock, norepinephrine has shown reduced mortality, or rates of refractory shock compared to dopamine or epinephrine. Data comparing dopamine and epinephrine was not found. Phenylephrine may worsen cardiogenic shock.

Distributive Shock

Norepinephrine vs Dopamine: Small trials of septic shock demonstrate norepinephrine outperformed dopamine in ability to maintain hemodynamic goals and increase oxygen delivery efficiency.[27,29,30,44,45] There was no significant difference in mortality between norepinephrine or dopamine in a subgroup analysis of septic patients from a large trial of ICU patients requiring vasopressors.[44]

Norepinephrine vs Epinephrine: In a randomized control trial of epinephrine (n = 169) vs norepinephrine +/- dobutamine (n = 161) in septic shock, there was no difference in mortality or arrhythmia. Epinephrine-treated patients had significantly lower pH and higher lactate during treatment.[46] Subanalysis of septic shock patients in a large randomized trial (N = 277) showed no difference in mortality or time to therapeutic goal between epinephrine (n = 76) and norepinephrine (n = 82).[35]

Norepinephrine vs Phenylephrine: Small trials of norepinephrine (n = 16) vs phenylephrine (n=16) in septic patients found phenylephrine increased lactic acid production and reduced creatinine clearance compared to norepinephrine, but there was no significant difference in hemodynamic parameters.[47,48] In a large multicenter evaluation of septic patients when there was a shortage of norepinephrine and alternatives were used, an increase in mortality was detected compared to historical controls.[49]

Summary: In distributive shock, small studies support that norepinephrine may outperform dopamine in maintenance of hemodynamics, through no difference in mortality has been seen in large trials. Norepinephrine appears equivalent to epinephrine but causes less metabolic derangements. Very little prospective data exists to support use of phenylephrine. Data were not found comparing dopamine, epinephrine, or phenylephrine to each other.

Safety

Norepinephrine: In a retrospective trial, hypokalemia and metabolic acidosis were more common in the norepinephrine-treated cohort compared to dopamine ($P<0.05$).[50] Norepinephrine has been shown to cause less metabolic derangement (lactic acid production, gastric malperfusion, metabolic acidosis) than both epinephrine and phenylephrine.[29,31,32,34-36,46,48]

Dopamine: Dopamine has been shown to cause more arrhythmia than norepinephrine in numerous trials of cardiogenic shock.[44,50,51] Dopamine use was associated with an increase in cardiac complication (ventricular tachycardia, troponin elevation, atrial fibrillation, heart rate > 130 or < 50) in an analysis of patients treated for shock related to spinal cord injury.[52] A similar analysis showed dopamine was associated with increased adverse effects in a subset of patients > 55 years.[53]

Epinephrine: Patients receiving 100 mcg boluses of epinephrine had a higher incidence of 24-hour mortality and cardiac arrest than historical case controls who would have qualified for treatment. This effect remained after adjustment for confounding variables.[6] Epinephrine has demonstrated more frequent metabolic disturbances compared to norepinephrine in numerous trials.[31-36] In a prospective observational cohort of patients requiring vasopressors for cardiogenic shock, epinephrine was the only vasopressor independently associated with increased 90-day mortality (OR 5.3; 95% CI, 1.88-14.7; $P = 0.002$).[54]

Phenylephrine: Phenylephrine use was associated with an increase in cardiac complication (ventricular tachycardia, troponin elevation, atrial fibrillation, heart rate > 130 or < 50) in an analysis of patients treated for shock related to spinal cord injury.[52,53]

Summary: Norepinephrine appears to cause less arrhythmia than dopamine. It also appears to have less effect on metabolic parameters, such as lactate production, than epinephrine. Phenylephrine and dopamine have been associated with higher rates of adverse effects in neurogenic shock.

Practicality

Norepinephrine: Can be purchased as a premix bag from compounding pharmacies or may be reconstituted to the desired concentration via a vial or ampule injected into an infusion bag. Premade infusions could be compounded at concentrations of 4 mcg/ml (1 mg in 250 ml) and 16 mcg/ml (4mg in 250 ml) and are stable in dextrose 5% or saline for 7 days at room temperature and ambient light.[55]

Dopamine: Available as an infusion directly from the manufacturer at varying concentrations, dopamine may be utilized without drug compounding. The shelf life of the premade bag is 18 months.[56]

Alternatively, an infusion may be compounded using stock vials and infusion bags to desired concentrations. Compounded infusions of 2 mg/ml, 10 mg/ml, and 30 mg/ml in normal saline, dextrose 5%, and dextrose 10% are stable for up to 84 hours under room temperature and ambient light.[57]

Epinephrine: Can be purchased as a premix bag from compounding pharmacies or may be reconstituted to the desired concentration via a vial or ampule injected into an infusion bag. Premade bags can be compounded at concentrations of 25 mcg/ml (5 mg in 250 ml), 50 mcg/ml (10 mg in 250 ml), and 100 mcg/ml (20 mg in 250 ml) in dextrose 5% or saline. These concentrations are stable for 30 days at room temperature and in ambient light.[58]

Phenylephrine: Can be purchased as a premix bag from compounding pharmacies or may be reconstituted to the desired concentration via a vial or ampule injected into an infusion bag. Phenylephrine is stable for 60 days at room temperature and light with concentrations of 200 mcg/ml (50 mg in 250 ml) and 400 mcg/ml (100 mg in 250 ml) in normal saline.[59]

DISCUSSION

Numerous factors must be considered when selecting a prehospital vasopressor. The agent should have utility in multiple shock states. Phenylephrine is limited in that it only stimulates $\alpha 1$, which may worsen cardiogenic shock.[38] Coupled with sparse clinical efficacy data, phenylephrine may be a less than ideal option as a "one-size-fits-all" vasopressor. This leaves agents such as dopamine, norepinephrine, and epinephrine. Premixed agents may be easier to administer in an uncontrolled ambulance environment. Premixed dopamine with a long shelf life is available from the manufacturer; however, all agents are available as premix solutions from compounding pharmacies. Ease of use should be balanced with pharmacologic profiles, efficacy, and safety data for each agent. While prehospital outcome data are lacking, extrapolation from inpatient shock management can provide initial direction.

Available evidence supports that norepinephrine has lower rates of refractory shock, mortality, and arrhythmia compared to dopamine.[44,43,44,50,51] Dopamine has the benefit of a more significant increased cardiac output compared to norepinephrine, which would be of benefit in bradycardic or cardiogenic shock. Despite this theoretical benefit, outcomes appear to be worse with dopamine in this shock type.[44] Worse outcomes with dopamine compared to norepinephrine in cardiogenic shock have been supported by other literature reviews as well. An English and Chinese language meta-analysis, which includes 5 studies not listed in this review, found dopamine-treated cardiogenic shock patients had higher 28-day mortality (RR 1.611; 95% CI, 1.219–2.129; $P < .001$) and higher risk of arrhythmia (RR 3.426; 95% CI, 2.130–5.510, $P < .001$) than norepinephrine.[60] Dopamine's inferior efficacy and concerning safety data may offset any benefit of its longer shelf life.

Epinephrine offers utility in numerous shock states, including septic, anaphylactic, and cardiogenic shock. Similar to dopamine, its pharmacologic profile provides a theoretical benefit in cardiogenic shock due to increasing cardiac output more than norepinephrine or dopamine. However, a small prospective trial has shown higher rates of refractory shock with epinephrine than norepinephrine in this population.[33] Epinephrine's association with increased mortality in cardiogenic shock also has been supported by other meta-analysis.[61] While it appears similar to norepinephrine in distributive shock, it more consistently causes metabolic derangement, such as lactate elevation, which may confound resuscitation.[31,32,35,36,46] Epinephrine's theoretical advantages in some shock etiologies, such as anaphylaxis, are difficult to reconcile against emerging data showing increased mortality in cardiogenic shock and prehospital transport patients.[6,33,54] Norepinephrine's large amount of supportive data, utility in all shock states, lower rates of arrhythmia, and ease of use with premixed infusions, make it a good option for use within an EMS system as a "one-size-fits-all" vasopressor.

One barrier to moving beyond a "one-size-fits-all" vasopressor strategy is the limited ability to evaluate the etiology of shock during medical transport. Patient evaluation is currently limited to paramedic assessment and physical exam findings. Advances in prehospital care may help revolutionize the assessment and management of shock patients in this setting. Prehospital ultrasound is currently being studied as a potential additional tool, which may help the prehospital provider better assess cardiac function and volume status.[62] Point-of-care testing also may be an option in certain EMS systems, which would allow for assessment of lactate, mixed venous oxygen partial pressure.[63] Expedient initiation of vasopressors for hemodynamic support has been associated with better neurologic outcomes in patients experiencing out-of-hospital cardiac arrest.[64] Advances in diagnostics, coupled with more sophisticated telemedicine, may lead to earlier identification of shock and initiation of hemodynamic support.[65] Future studies should attempt to characterize the types of shock frequently identified by EMS systems, as well as the shock states unlikely to survive to hospital admission without early vasopressor intervention.

Finally, the largest barrier to identifying an optimal vasopressor for nontraumatic prehospital shock is the complete absence of comparative evidence within prehospital populations. Comparative studies need to be completed evaluating clinical outcomes, such as survival to hospital admission, 30-day survival, rate of survival with good neurologic outcome, rates of cardiac arrhythmia, rearrest, and refractory shock in the prehospital setting. Current EMS systems that utilize multiple vasopressors should generate retrospective comparative data to aid in identifying an optimal agent. Data can be prospectively or retrospectively generated from EMS systems with a single vasopressor formulary that has changed to a different vasopressor. Like evaluations done in the ICU setting, retrospective outcome evaluations could be conducted amongst

cohorts of patients treated during times of different formulary vasopressor use.[50] Safety data surrounding the use of a vasopressor in an uncontrolled prehospital setting should also be generated. Rates of extravasation and dosing errors with infusions should be compared against other administration methods such as bolus dosing. There is still significant discovery to be made in the field of prehospital shock management. Those involved in EMS systems should evaluate their current practices to ensure they are providing the highest quality of care to their critically ill community members.

CONCLUSIONS

The robust evidence for use of norepinephrine in cardiogenic, distributive, and neurogenic shock from both efficacy and safety perspectives, numerous guideline recommendations, and ease of preparation make it a good option for prehospital use. More study is needed to identify an optimal strategy for prehospital hemodynamic support.

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