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REVIEW ARTICLE

Role of Vasopressor Administration in Patients with Acute Neurologic Injury

Katie M. Muzevich · Stacy A. Voils

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Abstract
Introduction Pharmacologic blood pressure elevation is often utilized to prevent or treat ischemia in patients with acute neurologic injury, and routinely requires administration of vasopressor agents. Depending on the indication, vasopressor agents may be administered to treat hypotension or to induce hypertension.
Methods Although numerous guideline statements exist regarding the management of blood pressure in these patients, most recommendations are based largely on Class III evidence. Further, there are few randomized controlled trials comparing vasopressor agents in these patients and selection is often guided by expert consensus.
Results We discuss the clinical evidence regarding vasopressor administration for blood pressure management in patients with acute neurologic injury. The effect of various vasopressors on cerebral hemodynamics is also discussed.
Conclusion Although high-quality clinical data are scarce, the available evidence suggests that norepinephrine should be considered as the vasopressor of choice when blood pressure elevation is indicated in patients with acute neurologic injury.

Keywords Vasopressor · Neurologic injury · Stroke · Subarachnoid hemorrhage · Traumatic brain injury · Carotid injury · Spinal cord injury · Hypertension · Blood pressure

K. M. Muzevich · S. A. Voils (✉)
Virginia Commonwealth University Health System,
Richmond, VA, USA
e-mail: svoils@mcvh-vcu.edu

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Introduction

Vasopressor administration is often utilized concurrently with fluid resuscitation in patients with acute neurologic injury to maintain or augment perfusion to areas of injury. Clinical outcomes may be poor when hypotension occurs in these patients. For example, a single systolic blood pressure of <90 mmHg has been shown to worsen outcomes in patients with traumatic brain injury. Administration of vasopressor agents is not a benign practice, however. In addition to other well-documented side effects, vasopressors increase cerebral blood flow and may lead to an increase in intracranial pressure (ICP) and cerebral edema. This is especially important in patients with acute neurologic injury because cerebral autoregulation is impaired in the area of injury.

Selection of vasopressor agent is frequently guided by the clinical characteristics of the patient as well as the goals of therapy. Consideration should also be given to the effect of vasopressors on cerebral hemodynamics (Table 1). However, caution should be utilized when interpreting these data because of variable methods used in measuring cerebral blood flow and differences in patient characteristics among studies. In this article, we review the evidence regarding the safety and efficacy of vasopressor administration for patients with traumatic brain injury, acute ischemic stroke, subarachnoid hemorrhage, acute spinal cord injury, and carotid disease.

Acute Ischemic Stroke

Patients with acute ischemic stoke (AIS) are more likely to present with arterial hypertension than arterial hypotension; however, the presence of hypotension (systolic blood

Table 1 Cerebral hemodynamic effects of vasopressors [19, 40, 41]

Drug	Mechanism	CBF	ICP	$CMRO_2$	$P_{bt}O_2$
Phenylephrine	Alpha-1 receptor agonist	↑	↑	↔	↔
Norepinephrine	Mixed alpha/beta-1-receptor agonist	↑	↔	↔	↑
Epinephrine	Mixed alpha/beta agonist	↑	NA	↑	NA
Dopamine	Dose dependent agonist: dopamine, beta and alpha receptors	↑	↔	↔	↔
Vasopressin	V-1 receptor agonist	↑	NA	↔	↑

CBF cerebral blood flow, *CMRO2* cerebral metabolic rate of oxygen consumption, *ICP* intracranial pressure, *NA* no available data, $P_{bt}O_2$ brain tissue oxygen tension

pressure <100 mmHg or diastolic blood pressure <70 mmHg) has been associated with neurological worsening, poor neurological outcomes, or death [1]. Guidelines recommend initial treatment with normal saline solution for volume expansion and correction of cardiac arrhythmias, which may interfere with cardiac output. If initial therapy fails to correct hypotension, a vasopressor such a dopamine is suggested as a reasonable adjunctive therapy [1].

Beyond the treatment of arterial hypotension, vasopressor therapy may be utilized in the setting of AIS to elevate blood pressure, a therapy that aims to increase cerebral perfusion pressure (CPP) to minimize expansion of the penumbra. Because of the lack of large clinical trial data with this approach, guidelines recommend against routine use of drug-induced blood pressure elevation for treatment of AIS outside the setting of clinical trials. However, in exceptional cases, vasopressor therapy may be utilized to increase cerebral blood flow [1]. One recent animal study showed an improvement in cerebral metabolic rate of oxygen in the core and penumbra as well as increases in collateral cerebral blood flow and oxygenation following administration of phenylephrine [2].

The optimal vasopressor for patients with AIS is controversial. Wityk suggests the ideal vasopressor should be available as an intravenous formulation, have rapid onset of action, be easily titratable, be devoid of adverse effects, and should not increase ICP; however, limited clinical trial data exist to support the use of one vasopressor over another [3]. A recent systematic review identified 12 trials utilizing vasopressor therapy for AIS. Two additional case reports utilizing phenylephrine were identified following the publication of the systematic review [4, 5]. Data from these trials are summarized in Table 2.

Despite the lack of robust clinical data, phenylephrine is the most widely studied agent for blood pressure elevation in AIS. The largest trial examining phenylephrine for this indication is a retrospective review, which aimed to determine the effect on morbidity and mortality as compared with no pharmacologic blood pressure elevation. Although fewer deaths occurred in the phenylephrine group, no statistically significant effect on morbidity or mortality was associated with use of phenylephrine. No serious adverse events were reported in either group [6].

Rordorf et al. subsequently conducted a prospective pilot study to determine if there was a subset of patients with AIS whom would benefit from elevation of blood pressure. Patients who presented within 12 h of AIS received increasing doses of phenylephrine to achieve a systolic blood pressure of at least 160 mmHg or that which was 20% above the admission systolic blood pressure, not to exceed 200 mmHg. Blood pressure elevation was continued for a maximum of 30 min. If the neurologic examination improved by at least 2 points on the National Institutes of Health Stroke Scale (NIHSS), phenylephrine was discontinued and blood pressure was allowed to return to baseline. Patients were then observed for an additional 20 min for signs of neurologic worsening. Responders were identified as patients who had a blood pressure "threshold" determined that below which, neurologic deterioration occurred. Daily attempts to wean phenylephrine were made for the responder group. A neurologist examined patients in a blinded fashion on and off of phenylephrine and the drug was continued if a change in neurologic exam occurred. Of the 13 patients enrolled in this trial, 7 experienced a 2-point increase in NIHSS score and no systemic or neurologic adverse events were observed [7].

Longer durations of pharmacologic blood pressure elevation in AIS have been reported [5, 6, 8–11]. A case report by Bogoslovsky reported a 3-point improvement in NIHSS when phenylephrine was used to increase mean arterial pressure (MAP) by 20% from baseline. Elevated MAP was maintained for 4 days then phenylephrine was tapered over a 2-day period [5].

Use of vasopressors to elevate blood pressure in normotensive patients with AIS remains controversial. To date, clinical guidelines do not support or provide recommendations for blood pressure elevation in normotensive patients with AIS. Data can be extrapolated from the few

Table 2 Clinical evidence supporting blood pressure augmentation with vasopressors in acute ischemic stroke

Author	Design	Intervention	Vasopressor dose	Titration goal	1° Outcome	Results	AE
Rordorf [6]	CC	Phenylephrine ($n = 30$) versus placebo ($n = 33$)	110 mcg/min (20–300 mcg/min)	Improved neurological deficit	Morbidity and mortality	No difference between groups	Paroxysmal a. fib (1/30)
Rordorf [7]	PI	Phenylephrine ($n = 13$)	40–300 mcg/min	SBP $\geq$ 160 or 20% $>$ baseline SBP (max 200)	Neurological improvement	7/13 improved NIHSS $\geq$2 points	None
Hillis [8]	CS	Phenylephrine ($n = 4$) versus IVF ($n = 2$)	Not reported	10% incremental MAP increases (max 130)	Lexical semantics	Improved perfusion to severely hypoperfused circumscribed areas; improved language tasks while MAP elevated	None
Hillis [9]	CR	Phenylephrine ($n = 1$)	Not reported	MAP 90–100	Language	Improved function	None
Hillis [10]	RT	Phenylephrine ($n = 9$) versus conventional treatment ($n = 6$)	Not reported	10–20% initial MAP increase; if no improvement, 10% incremental MAP increases until MAP of 130 or neurological improvement	Neurological improvement, cognitive score, tissue perfusion	Significant improvement from day 1 to day 3 in NIHSS score, cognitive score, and volume of hypoperfused tissue	None
Hillis [11]	CS	Phenylephrine ($n = 8$) or IVF ($n = 2$) versus conventional treatment ($n = 5$)	Not reported	10% incremental MAP increases until MAP of 130 or neurological improvement	Neurological improvement, cognitive score, tissue perfusion	6/6 who achieved perfusion goal had $\geq$3 point NIHSS improvement, compared to 2/9 who did not achieve perfusion goal	None
Bogoslovsky [5]	CR	Phenylephrine ($n = 1$)	Initial 8 mcg/min, to max 58 mcg/min	20% increased MAP	Neurological improvement	3-point NIHSS improvement	None
Stead [4]	CR	Phenylephrine ($n = 1$)	Initial 140 mcg/min	MAP 110–120	Neurological improvement	Complete resolution of left hemiparesis	None
Schwartz [42]	P	Norepinephrine ($n = 19$)	Initiated at 33 mcg/min with titration	MAP increase $\geq$ 10	CPP, ICP, V_m MCA	CPP 72.2–97 mmHg; V_m MCA increased 25.5 cm/s on affected side	Absolute ICP increase 0.19 mmHg
Marzan [43]	R	Norepinephrine ($n = 34$)	Mean 4 mcg/min (1–20 mcg/min)	SBP increase 10–20%	Safety and feasibility	9/34 improved NIHSS $\geq$2 points	Transformation to ICH (2/34); A. fib (1/34)
Meier [44]	RT	Epinephrine ($n = 37$) + low-molecular dextrans versus low-molecular dextrans ($n = 44$)	0.025–0.05 mg	3-, 5-min periods of SBP 210–220 mmHg, with 1 h between periods	Level of consciousness, severity of paresis, mortality at 21 days	Temporary improvement in level of consciousness (not statistically significant); increased survival in epinephrine group at 21 days ($P = 0.02$)	Patients who died within first 3 weeks had higher BP during first 3 days

Table 2 continued

Author	Design	Intervention	Vasopressor dose	Titration goal	1° Outcome	Results	AE
Oliviera-Filho [45]	CR	Dopamine ($n = 1$)	Not reported	SBP $>$ 160 mmHg	NIHSS	1-point NIHSS improvement from presentation score; 6-point improvement from worst score	Not reported

CC case control, *CS* case series, *CR* case report, *PI* pilot, *RT* randomized trial, *P* prospective, *R* retrospective, *SBP* systolic blood pressure, *NIHSS* National Institutes of Health Stroke Scale, V_m *MCA* peak mean flow velocity of the middle cerebral arteries, *MAP* mean arterial pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure

published clinical trials; however, these trials vary significantly in protocol, drug selection, and primary outcome. Most trials utilized phenylephrine and resulted in modest improvements in NIHSS scores, but larger prospective trials are necessary to confirm this observation.

Subarachnoid Hemorrhage

Delayed ischemic neurologic deficit (DIND) following cerebral vasospasm in patients with subarachnoid hemorrhage (SAH) is associated with significant morbidity and mortality. Although based largely upon uncontrolled studies, "triple H" therapy is routinely used to treat symptomatic vasospasm and involves induced hypervolemia, hypertension, and hemodilution. The importance of the individual constituents of this therapy is unclear; however, hemodilution remains the most controversial component. A recent study found that blood pressure elevation in these patients increased cerebral blood flow and brain tissue oxygenation while the hypervolemia/hemodilution components only mildly increased cerebral blood flow and negated the effects of hypertension on brain tissue oxygenation [12]. In patients with clinical or radiographically proven vasospasm, current practice commonly involves elevating blood pressure with fluids and vasopressors with a goal systolic blood pressure up to 180–220 mmHg (or MAP $>$130 mmHg) in patients with secured aneurysms [13, 14] (Table 3). Prophylactic induced hypertension as a component of triple H therapy has not been shown to decrease the incidence of DIND and should be discouraged [15–18]. Additionally, triple H therapy is not without potential risk. Myocardial ischemia, pulmonary edema, and heart failure have been reported and thus frequent assessment of cardiac enzymes, electrocardiograph, arterial blood pressure, fluid balance, chest X-ray, and central venous pressure should be performed to monitor for adverse effects related to triple H therapy [13].

The most commonly used vasopressors for triple H therapy are phenylephrine, dopamine, and norepinephrine, all of which have been shown to increase regional cerebral blood flow in SAH patients with ischemia [12]. Some authors recommend choice of vasopressor should depend on patient factors. For instance, patients with tachycardia at baseline should receive phenylephrine due to propensity to induce a reflex bradycardia. Conversely, patients with baseline bradycardia due to Cushing's reflex may benefit more from mixed alpha and beta agonists, such as norepinephrine and dopamine. Prospective comparative studies regarding vasopressor selection are lacking in this population. These authors recommend against the use of dopamine because of the arrhythmogenic potential that has been observed in clinical trials and unreliable effects of dopamine on cerebral blood flow [16, 19].

Table 3 Summary of blood pressure recommendations in patients with acute neurologic injury

Diagnosis	Blood pressure/cerebral perfusion pressure goal	Preferred agent(s)[a]	Guideline statement
TBI	CPP > 60 mmHg	Norepinephrine or phenyephrine	Brain Trauma Foundation: Guidelines for the management of severe traumatic brain injury, 3rd edition [25]
SCI	MAP > 85–90 mmHg first 7 days following injury	Norepinephrine or dopamine	American Association of Neurological Surgeons: Guidelines for the management of acute cervical spinal injuries [37]
ICH	CPP > 70 mmHg	Norepinephrine or phenylephrine	American Heart Association/American Stroke Association: Guidelines for the management of spontaneous intracerebral hemorrhage in adults [46]
SAH	Unsecured aneurysm: SBP 140–160 mmHg Secured aneurysm: SBP 180–220 mmHg or MAP > 130 mmHg[b]	Norepinephrine or phenylephrine	American Heart Association Stroke Council: Guidelines for the management of aneurysmal subarachnoid hemorrhage [13, 18]
AIS	No consensus; drug-induced hypertension may be attempted in "exceptional cases"	Norepinephrine or phenylephrine	American Heart Association/American Stroke Association Stroke Council: Guidelines for the early management of adults with ischemic stroke [1]

[a] Preferred agents based on author recommendations and expert consensus; see text for full discussion

[b] Guidelines do not state goal blood pressure; recommendations based upon expert consensus

AIS acute ischemic stroke, *CPP* cerebral perfusion pressure, *ICH* intracerebral hemorrhage, *MAP* mean arterial pressure, *SAH* subarachnoid hemorrhage, *SBP* systolic blood pressure, *SCI* spinal cord injury, *TBI* traumatic brain injury

Carotid Disease

Carotid endarterectomy (CEA) is a surgical procedure that is often performed to prevent stroke in symptomatic patients with atherosclerotic plaques at the carotid bifurcation. Carotid angioplasty with stenting (CAS) is a less invasive procedure that is being performed more frequently as an alternative to CEA. Postoperative hypotension is relatively common after both of these procedures with persistent hypotension occurring in approximately 20% of patients undergoing CAS. Hypotension presumably occurs due to increased compliance and stretch in the carotid baroreceptors following plaque removal or stent placement. Risk factors for hypotension include general versus regional anesthesia [20] and perioperative administration of angiotensin converting enzyme inhibitors or angiotensin receptor blockers [21].

A recent study examined the risk factors for hypotension requiring vasopressor administration in patients undergoing CAS [22]. Multivariate analysis showed that both female sex and age >80 years was associated with an increased risk of prolonged vasopressor administration (>24 h). Vasopressor administration for a shorter duration (≤24 h) was more common in patients with a history of myocardial infarction regardless of age or sex.

Selection of vasopressor agents in treating refractory post-operative hypotension is mostly anecdotal in this population. Because bradycardia often co-exists with hypotension, dopamine has been utilized most commonly. Recently, a retrospective study in patients undergoing CAS compared outcomes in patients who received dopamine, norepinephrine, or phenylephrine for refractory hypotension [21]. Patients who received dopamine tended to have longer infusion times and more arrhythmias than patients receiving phenylephrine or norepinephrine. The authors conclude that agents with predominately alpha-adrenergic effects should be used preferably in this population. The retrospective nature and small sample included in this study make it difficult to make definitive conclusion regarding vasopressor selection.

In patients with persistent neurologic deficits following CEA, some authors recommend fluids and vasopressors to elevate systolic blood pressure >180 mmHg [23]. A potential risk of hypertension in patients undergoing CEA has been termed cerebral hyperperfusion syndrome. Vascular headache, eye pain, intracerebral hemorrhage, or seizures may occur as a result of return of circulation to an area with loss of autoregulation due to chronic ischemia. This is thought to be related to significant contralateral carotid artery stenosis, degree of hypertension, or increased intraoperative cerebral perfusion. In a recent review, however, contralateral CEA performed within the past 3 months was the only predictive variable for development of cerebral hyperperfusion syndrome [24].

Traumatic Brain Injury

Systemic hypotension increases morbidity and mortality in patients with traumatic brain injury (TBI) [25], therefore, it is recommended that systolic blood pressures less than 90 mmHg be avoided. On this pretense, it has been hypothesized that elevating MAP may also improve outcome; however, clinical evidence does not support routine use of this practice. Despite uncertainty regarding the ideal MAP, it is recommended that CPP be maintained above 60 mmHg [25]. Higher CPP may be beneficial; however, use of fluids and vasopressors to maintain CPP greater than 70 mmHg has been associated with increased incidence of acute respiratory distress syndrome (ARDS) and hence is discouraged [26]. Additionally, experimental data have shown that vasopressor administration to elevate CPP may worsen cerebral edema by increasing ICP in patients with TBI and impaired autoregulation [25].

The ideal agent for increasing MAP and thus CPP remains unknown. Animal studies have utilized norepinephrine [27–30], phenylephrine [31, 32], dopamine [26, 28, 30], and vasopressin [31]; however, data in humans are limited to norepinephrine [19, 33, 34], dopamine [19, 33, 35], and phenylephrine [35, 36]. The largest published trial utilizing vasopressor therapy in patients with TBI sought to compare the effects of a cerebral blood flow based management strategy as compared to an ICP-based strategy. The frequency of jugular venous desaturations and refractory elevations in ICP were compared as well as long-term neurologic outcome. Both groups utilized dopamine and/or phenylephrine for blood pressure elevation, although the threshold for vasopressor initiation and goal MAP differed between groups. The study concluded that the cerebral blood flow-targeted protocol significantly reduced the frequency of jugular desaturation, although this did not result in improved neurologic outcomes and was associated with a five-fold increase in the frequency of ARDS [35]. Logistic regression analysis suggested that administration of epinephrine (which was not part of either protocol, but was utilized in several patients), administration of high dose dopamine (defined as greater than the median administered dose) and a history of drug abuse were associated with the development of ARDS [26].

Although no evidence exists to support the notion that selection of vasopressor impacts morbidity or mortality in patients with TBI, cerebrovascular effects vary among vasopressors. In a prospective study by Ract et al., 19 patients with severe head injury (GSC $\leq$ 8) underwent evaluation of cerebral hemodynamics (MAP, CPP, ICP, heart rate, aortic output, jugular venous oxygen saturation, and cerebral blood flow velocity of the M1 segment of the middle cerebral artery) while receiving dopamine as compared to norepinephrine. For the same MAP, ICP was significantly higher with dopamine than norepinephrine with no increase in cerebral blood flow [33]. A similar prospective, randomized, crossover trial by Steiner et al. evaluated the cerebrovascular effects of norepinephrine as compared to dopamine. Although there were no differences between absolute values of flow velocity or ICP between the two drugs at any CPP, the trial may have been underpowered to detect such a difference. Norepinephrine produced predictable and significant increases in flow velocity, whereas changes with dopamine were inconsistent [19]. Based on limited clinical data and the cerebral hemodynamic profile of the respective vasopressors, norepinephrine, and phenyleprine appear to be the preferred agents when blood pressure elevation is indicated in patients with TBI.

Spinal Cord Injury

Systemic hypotension frequently occurs after acute SCI due to several factors such as hypovolemia and, depending on the level of the injury, direct spinal cord trauma and loss of sympathetic vasomotor control. Denervation to the cardiac accelerator fibers at thoracic spinal nerves 1 through 6 may result in bradycardia and hypotension. Similar to TBI, there may be a loss of autoregulation in spinal cord blood flow, or the ability to deliver a consistent amount of oxygen to the spinal cord at differing levels of pressure. Although this has not been evaluated prospectively, a decrease in blood pressure may be expected to decrease perfusion to the spinal cord causing hypoxia and theoretically worsen the severity of the initial injury (secondary injury).

Guidelines in patients with acute cervical spinal injuries summarize results from six case series in which blood pressure was maintained or elevated in patients with acute SCI. In the absence of robust clinical data, systolic blood pressure less than 90 mmHg should be avoided or corrected as soon as possible after SCI, as laboratory evidence suggests that hypotension contributes to secondary injury after acute SCI by further reducing spinal cord blood flow and perfusion. In addition, it is recommended that a goal MAP of 85–90 mmHg be achieved and maintained for the first 7 days following injury [37]. Thus, vasopressors may play a dual role in management of these patients: treatment of hypotension acutely, and maintaining perfusion to the penumbra for an arbitrary period of time after injury.

In patients with acute SCI, adequate intravascular access should be obtained upon admission to include central line access to assess filling pressures and arterial line access for accurate blood pressure assessment. Although no algorithm exists to guide blood pressure management after SCI, volume expansion is usually attempted prior to vasopressor

administration. Additionally, lower extremity wraps or trousers may prevent venous pooling due to loss of muscle tone. As patients with SCI often experience bradycardia, a vasopressor with activity at beta-receptors (dopamine) is favored over those with selective alpha-activity (phenylephrine), or presumably those active at vasopressin receptors (vasopressin) [37]. Although clinical data are lacking, case reports have documented efficacy of oral vasopressor agents such as midodrine (a selective α-1 agonist) at a dose of 10 mg three times daily [38]. However, midodrine should be used with caution in this population due to reports of urinary retention [39]. Use of the sympathomimetic amine ephedrine is also common; however, little evidence exists to support this therapy.

Discussion

Blood pressure elevation in the setting of acute neurological injury is a strategy hypothesized to prevent further ischemic injury. For most patients with neurologic injury, adequate fluid resuscitation should precede initiation of a vasoactive drug. Based on cerebral hemodynamic profile, norepinephrine may be a suitable agent for blood pressure elevation in many circumstances, as it increases cerebral blood flow and brain tissue oxygen tension while maintaining a neutral effect on ICP and cerebral metabolic rate of oxygen (Table 1). However, this theory is untested in comparative, well-designed clinical trials.

Specific blood pressure goals vary for different types of neurologic injury and often must be extrapolated from limited published clinical data (Table 3). Further, this practice is not universally accepted, such as with AIS, where blood pressure elevation in normotensive patients is recommended only under "exceptional cases" [1]. Although many guideline statements address basic principles of blood pressure management, most recommendations regarding this practice are based on Class III evidence and few provide recommendations regarding vasopressor selection.

The use of blood pressure elevation in patients with acute neurologic injury remains controversial, as much of clinical data supporting this concept exist as small trials and case reports, which utilized surrogate endpoints to assess outcome. Continued research in this area is needed in the form of prospective, randomized, trials with primary outcomes such as functionality at 6 months, ability to perform activities of daily living, and mortality. Fortunately, a number of ongoing clinical trials address blood pressure management in patients with neurologic injuries. For example, a phase II, multicenter trial comparing intravenous fluid fluids, phenylephrine, and/or norepinephrine to elevate MAP in patients with AIS was recently completed, and a randomized, controlled, open-label clinical trial comparing vasopressin and catecholamines for CPP augmentation in patients with TBI is actively recruiting subjects. Results of these trials may provide some valuable insight regarding the role of vasopressors for blood pressure elevation in patients with acute neurologic injury.

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