EDITORIALS

Treating Shock — Old Drugs, New Ideas

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Circulatory shock is a medical emergency that is characterized by hypotension and decreased tissue perfusion; if left untreated, it can lead to irreversible cellular injury and death. Hypotension associated with shock can be the result of any of a number of factors, depending on the type of shock; these include biventricular dysfunction, intravascular hypovolemia, and the vascular effects of inflammatory responses. Irrespective of the underlying cause of shock, the treatment includes initial resuscitation with vasopressors, volume expansion (performed cautiously in patients with heart failure), and additional therapy for multiorgan system dysfunction, concomitantly with correction of the underlying cause. A critical question is which vasopressor should be used initially. The answer is complicated by the difficulty in conducting prospective, randomized trials involving acutely ill patients.

Clinicians make an initial choice of vasopressor on the basis of published guidelines, individual experience, and institutional bias. Dopamine, the precursor for norepinephrine in the sympathetic nervous system, is recommended as a first-line agent.[1,2] However, patients in shock may have a diminished response to indirect-acting agents such as dopamine.[3] In the case of patients with heart failure, a large component of the response to dopamine is neuronal release of norepinephrine.[3] When endogenous norepinephrine is depleted in shock states, indirect-acting agonists such as dopamine are less able to produce this response.[3] In this setting, direct-acting agents such as epinephrine or norepinephrine may have improved efficacy. Epinephrine is used for resuscitation and to treat anaphylaxis, but its β_2-adrenergic effects can cause hyperglycemia, acidosis, and other adverse effects. Norepinephrine is an endogenous α_1-adrenergic vasoconstrictor and a β_1-adrenergic agonist that is stored in the sympathetic nerve terminal. In recent years, vasopressin has been increasingly used to treat the hypotension associated with shock.[4] Vasopressin may be particularly effective in reversing mediator-induced vasodilatory shock in patients with sepsis or anaphylaxis.[4,5]

In this issue of the *Journal*, De Backer et al. report the results of a multicenter trial in which they randomly assigned 1679 patients to receive either dopamine or norepinephrine as first-line vasopressor therapy to treat circulatory shock.[6] The type of shock that occurred most frequently was septic shock (1044 patients, 62.2%), followed by cardiogenic shock (280 patients, 16.7%) and hypovolemic shock (263 patients, 15.7%). The primary outcome was the rate of death at 28 days after randomization; secondary end points included adverse events and the number of days without need for organ support. The use of corticosteroids was similar in the two groups (40.1% of patients in the dopamine group and 39.7% of those in the norepinephrine group), as was the use of activated human protein C in patients with septic shock (18.8% in the dopamine group and 19.1% in the norepinephrine group). There was no significant difference in the rate of death at 28 days between patients who were treated with dopamine (52.5; 95% confidence interval [CI], 49.2 to 55.9) and those who were treated with norepinephrine (48.5; 95% CI, 45.1 to 51.9). However, arrhythmias were more frequent in the dopamine group than in the norepinephrine group (24.1% vs. 12.4%, $P<0.001$), and among the patients with cardiogenic shock, the rate of death at 28 days was higher among those treated with dopamine than among those treated with norepinephrine ($P=0.03$ by Kaplan–

Meier analysis). The authors conclude that their study raises serious concerns about the safety of dopamine as a first-line therapy for shock.[6]

Two important limitations of this study are worth noting. First, the authors defined the adequate administration of fluids as at least 1 liter of crystalloids or 500 ml of colloids, unless hemodynamic monitoring suggested otherwise. This seems to be a relatively low amount of fluid, especially since 78% of the patients were in septic or hypovolemic shock, and correction of hypovolemia is an important initial therapy. Various degrees of volume depletion must have existed in this diverse patient population, and therapeutic goals for volume repletion are difficult to set and achieve with standard hemodynamic monitoring. The type and amount of volume resuscitation may have affected the outcomes. Second, the authors suggest that they used "equipotent" doses of vasopressors, equating 20 μg per kilogram of body weight per minute of dopamine with 0.19 μg per kilogram per minute of norepinephrine. Evidence that these doses of the two vasopressors are equipotent does not exist.

An additional question is how the authors defined the resolution of shock. The criteria for entry into the study included the presence of clinical signs of tissue hypoperfusion, such as altered mental state, mottled skin, oliguria, or blood lactate levels higher than 2 mmol per liter. However, the authors do not clearly state how they defined the resolution of shock — a process that may take varying amounts of time depending on the type of shock.

What are the clinical implications of this study? The data challenge consensus guidelines that recommend dopamine as the initial vasopressor for increasing arterial pressure in the case of septic shock[1] or cardiogenic shock.[2] A previous observational study involving 1058 patients in shock reached a similar conclusion, showing that dopamine administration was an independent risk factor for death in the intensive care unit.[7] Studies also consistently show that tachycardia is a frequent side effect of dopamine therapy.[7,8]

In addition, norepinephrine needs to be considered as an initial therapeutic agent for patients in circulatory shock. Norepinephrine has long been used as a first-line agent for the treatment of hypotension and shock among patients in intensive care units and among those who have just undergone cardiac surgery. Despite concerns regarding vasoconstriction in end organs, when norepinephrine was infused to achieve a mean arterial blood pressure of higher than 70 mm Hg in patients with sepsis, urine flow and creatinine clearance rate increased after 24 hours.[9]

A remaining question is the role of arginine vasopressin as a therapeutic agent for shock. De Backer et al. used vasopressin or epinephrine as rescue therapy, and only two patients in each group received vasopressin. Vasopressin is another direct-acting agent (acting on V1 and V2 receptors) that may be as effective as norepinephrine in restoring blood pressure in patients with circulatory shock, without the tachycardia associated with dopamine. Previous studies have compared norepinephrine and vasopressin among patients with septic shock.[8,10] A recent study in the *Journal* showed that low-dose vasopressin was effective, and among patients with septic shock who were treated with catecholamines, there was no difference in the rate of death between those who received vasopressin and those who received norepinephrine.[10] There are also reports of a benefit of vasopressin therapy among patients in anaphylactic shock, since this drug is able to reverse mediator-induced vasoplegia.[5] However, when a patient presents with circulatory shock, other reversible causes should always be considered, including pneumothoraxes, pericardial tamponade, and adrenal insufficiency.

Historically, there is a widespread clinical perception that the use of norepinephrine in patients with shock may increase the risk of death. As shown in the study by De Backer et al., shock from any cause carries a high risk of death, and vasopressors are temporizing agents that are administered until the underlying cause has been treated or the shock has resolved. The results of the study by De Backer et al. should also put an end to the outdated view that the use of norepinephrine increases the risk of death.

Financial and other disclosures provided by the author are available with the full text of this article at NEJM.org.

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Ethosuximide in Childhood Absence Epilepsy — Older and Better

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Where did our wisdom about treating epilepsy originate? The ketogenic diet came from ancient teachings. The mistaken belief that seizures were caused by sexual excess led to bromides. Modern medications are developed through screening processes and, now, by drug design. However, establishing the actual clinical efficacy of a specific treatment is quite difficult. In most seizure disorders, a treatment is assumed to have resulted in optimal control if no seizures occur over a considerable period of observation. The patient and the physician cross their fingers and tick off the seizure-free days, weeks, and months before deeming a treatment successful. But the determination of therapeutic efficacy in epilepsy is different from that in many other medical conditions, such as hypertension, infection, or diabetes, in which clinicians can measure blood pressure, check a culture, or measure blood glucose levels.

Where do we obtain credible evidence that a certain medication is the right one for someone who has seizures? How are our prescribing habits formed? Finding answers to these questions is not a simple process.[1] We are influenced by the wisdom of mentors, textbooks, observational studies, standards established by professional organizations, and careful (but often clinically irrelevant) studies designed to demonstrate efficacy to the Food and Drug Administration.

Recognizing this challenge, Glauser and colleagues conducted a study of drug therapies for childhood absence epilepsy in which success could be measured more definitively and in a timely manner, and they report the results in this issue of the *Journal*.[2] Their double-blind, randomized trial compared the efficacy, adverse-event profile, and attentional effects of ethosuximide, valproic acid, and lamotrigine in children with previously untreated absence epilepsy. No studies have conclusively demonstrated efficacy of any drug treatment in this disorder. This common epilepsy syndrome is one in which there could be an objective end point: freedom from treatment failure. The authors defined failure as the persistence of absence seizures, as well as a number of other important outcomes, including a generalized tonic–clonic seizure, excessive drug-related systemic toxicity, dose-limiting toxicity, and the desire of the parents or physician to simply withdraw the study treatment. The three study medications were chosen because they are the agents most commonly prescribed and because their use has spanned decades — from the oldest (ethosuximide) to the newest (lamotrigine).

One particular advantage of studying absence epilepsy is that the clinician can induce hyperventilation at the bedside to determine whether the child is still subject to seizures and can also rely on the sensitivity of an electroencephalogram. In this study, the researchers were able to objectively measure another important aspect of therapy — that is, whether the medication interferes with the patient's attentiveness. They concluded that ethosuximide was the optimal initial therapy for children with childhood absence epilepsy in terms of both seizure control and attentional effects. Their work meets critical criteria for clinical as well as statistical relevance.