

Vasopressin During Uncontrolled Hemorrhagic Shock: Less Bleeding Below the Diaphragm, More Perfusion Above

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In 1990, about 5 million people died worldwide as a result of injury, and it seems likely that the global epidemic of deadly trauma is only beginning. By 2020, deaths from injury are expected to increase to 8 million worldwide (2), and 30% of these fatalities will be attributable to uncontrolled hemorrhagic shock (3). Resuscitation of patients in uncontrolled hemorrhagic shock remains one of the most challenging aspects of emergency care, and trauma patients with complete cardiovascular collapse have an extremely poor chance of survival. For example, in a 1993 study of 138 trauma patients requiring cardiopulmonary resuscitation at the accident scene or during transport, none of the initially successfully resuscitated patients survived to hospital discharge (4). Accordingly, prevention of cardiac arrest has been considered to be the primary goal of trauma care (5). Unfortunately, trauma-related cardiac arrest is only the tip of the iceberg. Because hemorrhage-induced hypotension in trauma patients is predictive of frequent mortality and morbidity (6), fighting prolonged hypotension may be equally important.

For hemodynamic stabilization of critically injured patients with uncontrolled hemorrhagic shock current trauma guidelines recommend infusion of crystalloid or colloid solutions in addition to catecholamine vasopressors. In a large clinical study of penetrating

torso trauma, patients receiving delayed fluid resuscitation had better survival rates than those receiving immediate fluid resuscitation (7). Roberts et al. (8) further found no scientific evidence for the effectiveness of immediate fluid resuscitation in uncontrolled hemorrhagic shock. And a Cochrane review of randomized controlled trials found no evidence either for or against early or large volume IV fluid administration in uncontrolled hemorrhage (9). At present, therefore, we have no clearly proven fluid resuscitation strategy for uncontrolled hemorrhagic shock, and it seems expedient to consider alternative strategies to prevent immediate or delayed cardiac arrest in these patients.

There are experimental and clinical data showing promising effects of infusing vasopressin in severe hemorrhagic shock. For example, vasopressin improved short- and long-term survival in a porcine model of uncontrolled hemorrhagic shock after penetrating liver trauma (10,11). In patients with intraabdominal bleeding and subsequent shock which was unresponsive to volume replacement, vasopressin was reported to be beneficial to stabilize cardiocirculatory status almost 20 yr ago (12). In addition to the strong vasopressor effect of vasopressin during catecholamine-refractory shock, another beneficial effect of vasopressin may be that blood is shifted away from a given subdiaphragmatic site of injury to the heart and brain, thus decreasing bleeding and optimizing vital organ perfusion. This specific effect of vasopressin may be especially life-saving in patients with uncontrolled hemorrhage resulting from subdiaphragmatic injury. In agreement with this hypothesis, we observed beneficial effects of vasopressin in both blunt and penetrating trauma patients with uncontrolled hemorrhagic shock (13) and were able to resuscitate a blunt trauma patient with uncontrolled hemorrhagic shock (14).

Despite these promising observations, some researchers are concerned about vasopressin-related problems such as negative cardiac inotropy and myocardial ischemia (15,16), and others have questioned

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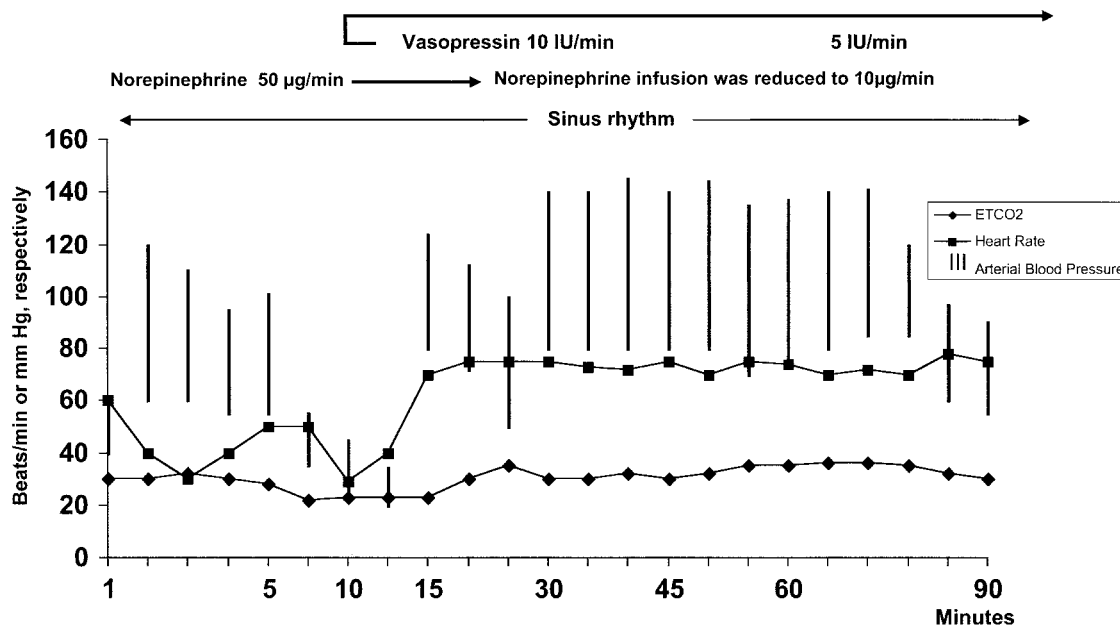


Figure 1. Drug dosages may appear excessive as a result of uncontrolled hemorrhagic shock and massive infusion of fluids. Note that timeline is not to scale. Reprinted with permission from Springer-Verlag, Heidelberg, Germany (13).

the clinical value of results obtained with vasopressin in shock studies. However, extrapolating side effects of vasopressin observed during normal cardiocirculatory function with an intact baroreflex into the shock setting with autonomic insufficiency (17) may not be correct. In addition, when discussing the complications of vasopressin, it is easily forgotten that the dose used makes a great difference; for example, patients in vasodilatory shock (with autonomic insufficiency) can be successfully treated with a vasopressin infusion of about 2 to 6 U/h (18,19), whereas patients presenting with upper intestinal bleeding need bolus dosages that are approximately 5 times larger (20).

In this issue of *Anesthesia & Analgesia*, Sharma and Setlur (21) present a case report of two patients suffering from uncontrolled hemorrhagic shock whose hypotension persisted even after normovolemia was achieved with transfusion of blood and catecholamines, suggesting severe vasoplegia. Interestingly, when vasopressin was infused, arterial blood pressure rapidly normalized, thus enabling long-term survival. The underlying mechanism was probably a preserved vascular reactivity to vasopressin in catecholamine-refractory shock, therefore facilitating vasoconstriction. This is in agreement with a study from Morales et al. (22) in canines with normovolemic vasoplegia after hemorrhagic shock, in which large doses of catecholamines were unable to reverse hemorrhagic shock but additional infusion of vasopressin effectively restored cardiocirculatory function. In the cases described by Sharma and Setlur (21), with continuing aggressive fluid resuscitation (total cumulative fluids, 17 L and 30 L, respectively) but attenuated

catecholamine effects, a vasopressin infusion then facilitated cardiovascular stabilization, indicating that vasopressin may be an option to bridge difficult hemodynamic situations, as in septic shock (18,19). These observations suggest that endogenous vasopressin insufficiency may be an underlying mechanism of refractory hypotension after prolonged hemorrhagic shock—a new phenomenon, at least in hemorrhagic shock patients, but similar to experiences in cardiac arrest and septic shock.

Interestingly, both patients in these case reports (21) received a combination of vasopressin and catecholamines during the late phase of uncontrolled hemorrhagic shock, which may be more effective than either drug alone. This enhancing effect of a combination of vasopressin and catecholamines is in agreement with our evidence in settings of severe shock such as cardiac arrest and septic shock (1,13,14,18,23–25). Furthermore, these case reports demonstrate that prolonged hemorrhagic shock with severe hypotension managed with vasopressin can result in fully conscious patients with intact cardiocirculatory function and full neurological recovery. This is in agreement with a case report (13) of a patient with multiple fractures of the pelvis, spine, and legs, as well as a severe head trauma after a fall from a roof (fourth floor), resulting in uncontrolled hemorrhagic shock and severe hypotension that was refractory to massive infusion of fluids and norepinephrine. Subsequent infusion of vasopressin prevented cardiocirculatory collapse, resulted in a stable hemodynamic function, and enabled emergency surgery. This patient made a full neurological recovery (Fig. 1) (13).

These case reports (13,14,21,26) provide valuable information because the successful treatment of uncontrolled hemorrhagic shock with vasopressin was reproducible and reported by different observers. We believe that in patients with uncontrolled hemorrhagic shock, infusing vasopressin may be an option to stabilize cardiocirculatory function and prevent cardiac arrest. In the absence of randomized controlled trials investigating the role of vasopressin in uncontrolled hemorrhagic shock today, even the currently limited clinical data available may support treatment decisions in selected patients who would otherwise rapidly die. In the future, we need to assess whether the existing laboratory (10,11,27) and limited clinical (13,14,21) data on treating uncontrolled hemorrhagic shock successfully with vasopressin can be confirmed in a randomized controlled clinical trial. In addition, the best timing of application and optimal dose of this form of therapy need to be addressed.

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