

Early Use of Vasopressors After Injury: Caution Before Constriction

Jason L. Sperry, MD, MPH, Joseph P. Minei, MD, Heidi L. Frankel, MD, Micheal A. West, MD, PhD, Brian G. Harbrecht, MD, Ernest E. Moore, MD, Ronald V. Maier, MD, and Ram Nirula, MD, MPH

Objective: Recent evidence suggests that overly aggressive crystalloid resuscitation is associated with poor outcome. This has led to a renewed interest in the use of vasopressors for hemodynamic support during resuscitation after injury. We sought to characterize early vasopressor (EV) use and aggressive early crystalloid resuscitation (ECR) and their association with mortality in severely injured patients.

Methods: Data were obtained from a multicenter, prospective, cohort study designed to evaluate the outcome of blunt injured adults in hemorrhagic shock. Early deaths (<48 hours) were excluded from the analysis. A single Cox propor-

tional hazard regression model was used to evaluate the effects of EV use (levophed, phenylephrine, dopamine, or vasopressin) and aggressive ECR on mortality at 12 and 24 hours postinjury, while controlling for important physiologic, injury, resuscitation, and patient demographic confounders.

Results: Cox proportional hazard regression revealed that EV use within 12 hours after injury was independently associated with over an 80% higher risk of mortality (hazard ratio [HR] 1.81, 95% confidence interval [CI] 1.1–2.9, $p = 0.013$), and was independently associated with over a twofold higher risk of mortal-

ity at 24 hours (HR 2.15, 95% CI 1.4–3.4, $p = 0.001$). These findings were consistent across all vasopressor subtypes. Aggressive ECR was independently associated with a 40% reduction in mortality (HR 0.594, 95% CI 0.37–0.95, $p = 0.030$).

Conclusion: These findings provide evidence that the early use of vasopressors for hemodynamic support after hemorrhagic shock may be deleterious, and should be used cautiously and not in place of aggressive crystalloid resuscitation after severe blunt injury.

Key Words: Vasopressor therapy, Crystalloid resuscitation, Cox proportional hazard regression.

J Trauma. 2008;64:9–14.

Overly aggressive fluid resuscitation after elective general surgery, injury, and critical illness has been linked to worse outcomes.^{1–4} Specifically, excessive fluid administration has been implicated as a causative factor in coagulation disturbances,^{5,6} abdominal compartment syndrome,⁷ pulmonary and cardiac dysfunction,^{2,4,8,9} gastrointestinal ileus, and bowel anastomotic complications.^{2,10} Experimental evidence also suggests that increases in extracellular volume and changes in cellular osmolarity results in cytosolic acidification, disturbances of cellular phosphorylation, and an in-

creased production of proinflammatory mediators.^{11–15} This accumulating evidence has led to a renewed interest in moderation of crystalloid resuscitation and a shift toward the early use of vasopressors for hemodynamic support after injury.¹

Animal research has provided support for this renewed interest in early vasopressor (EV) therapy for hemorrhagic shock.¹⁶ Beneficial effects of both arginine vasopressin and phenylephrine, as compared with crystalloid alone, have been found in traumatic brain injury,^{17,18} pulmonary contusion,¹⁹ and hemorrhagic shock animal models.^{20–22} However, the clinical outcomes associated with EV use within the first 24 hours from injury have not been adequately characterized in humans. The specific aim of the current analysis was to characterize EV use and aggressive early crystalloid resuscitation (ECR) and their potential effect on mortality after severe traumatic injury and hemorrhagic shock.

METHODS

Data were derived from the ongoing multicenter prospective cohort study known as the Inflammation and the Host Response to Injury, a large-scale collaborative program supported by the National Institute of General Medical Sciences, which is designed to characterize the genomic and proteomic response in injured patients at risk for multiple organ failure after traumatic injury and hemorrhagic shock.²³ Standard operating procedures were developed and implemented across all institutional centers to minimize variation in postinjury care, including early goal-directed resuscitation and management of shock, strict glycemic control, venous

Submitted for publication July 29, 2007.

Accepted for publication October 11, 2007.

Copyright © 2008 by Lippincott Williams & Wilkins

From the Division of Burn, Trauma, Critical Care (J.L.S., J.P.M., H.L.F., R.N.), University of Texas Southwestern Medical Center, Dallas, Texas; Division of Trauma and Critical Care (M.A.W.), Department of Surgery, Northwestern University, Chicago, Illinois; Department of Surgery (B.G.H.), University of Louisville, Louisville, Kentucky; Department of Surgery (E.E.M.), Denver Health Medical Center and the University of Colorado Health Sciences Center, Denver, Colorado; and Division of General Surgery and Trauma (R.V.M.), Harborview Medical Center and the Department of Surgery, University of Washington.

Supported by the National Institutes of Health Grant NIH NIGMS U54 GM062119-1.

Presented as a poster at the 66th Annual Meeting of the American Association for the Surgery of Trauma, September 27–29, 2007, Las Vegas, Nevada.

Address for reprints: Jason L. Sperry, MD, MPH, Division of General Surgery, Department of Surgery, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213; email: sperryjl@upmc.edu.

DOI: 10.1097/TA.0b013e31815dd029

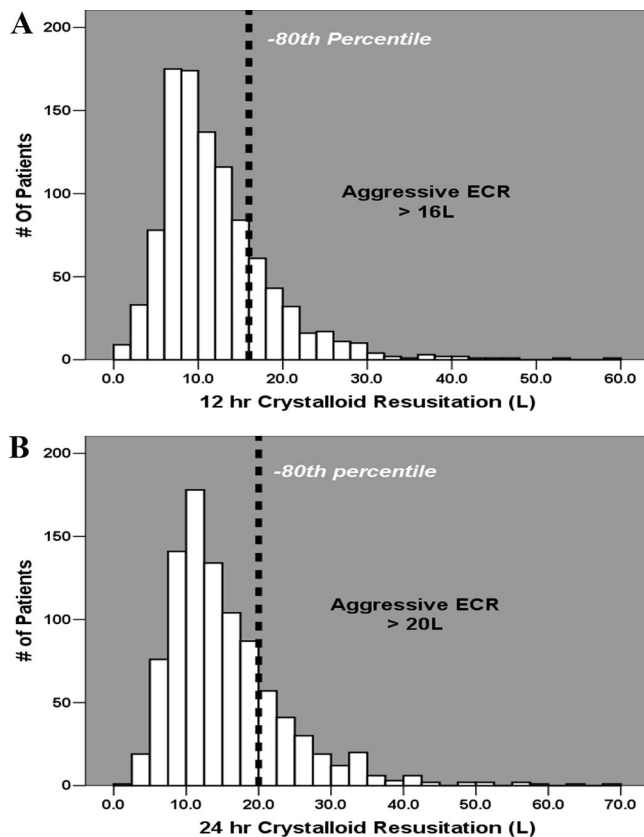


Fig. 1. Histogram depicting volume of crystalloid resuscitation at 12 (A) and 24 hours (B) postinjury for the entire cohort.

thromboembolism prophylaxis, appropriate low tidal volume ventilation, ventilator-associated pneumonia management, and restrictive transfusion protocols.^{23–27} Patients admitted to one of the seven institutions, during a 3.5-year period (November 2003 to March 2007), were included in the analysis. Inclusion criteria included blunt mechanism of injury, presence of prehospital or emergency department systolic hypotension (<90 mm Hg) or an elevated base deficit (≥ 6 meq/L), blood transfusion requirement within the first 12 hours, and any body region exclusive of the brain with an abbreviated injury score ≥ 2 , allowing exclusion of patients with isolated traumatic brain injury. Patients aged <16 or >90 years and those with cervical spinal cord injury were also excluded from enrolment. Patients who would be considered unsalvageable and who died within the first 48 hours from injury were excluded for the current analysis to eliminate patients who had vasopressors started as a penultimate maneuver. Clinical data were entered and stored in TrialDb, a web-based data collection platform, by trained research nurses.²⁸ Integrity of the data were maintained through ongoing curation and external data review by an independent chart abstractor.

A single Cox proportional hazard regression model was used to evaluate the effects of EV use and ECR on mortality, while controlling for important physiologic, injury, resuscitation, and patient demographic confounders. All time variables for mortality were determined from the day of initial injury. The model evaluated EV use and ECR at both 12- and

24-hour time points after injury. The model was also then stratified by age (≤ 55 years vs. >55 years) to determine whether any mortality risk associated with the two covariates of interest was age dependent. Those vasopressors with a considerable vasoconstrictor effect (phenylephrine, norepinephrine, dopamine, and vasopressin) were used for determination of the EV variable, whereas those with primary inotropic effects (epinephrine, dobutamine, milrinone) were not considered in this analysis and were categorized in the No EV group. The risk of mortality attributable to each individual vasopressor was also determined. Crystalloid resuscitation greater than 16 L and 20 L at 12 hours and 24 hours, respectively, was considered aggressive ECR, based on being above the 80th percentile for volume of crystalloid resuscitation for the entire cohort (Fig. 1A and B). It was assumed that those patients receiving crystalloid volume above this 80th percentile threshold would be at highest risk for iatrogenic complications secondary to overly aggressive resuscitation.

Potential confounders in the final model included patient age, gender, hospital center, injury severity score (ISS), presenting Glasgow Coma Scale score, hypotension at arrival (systolic blood pressure <90 mm Hg), comorbidities (history of myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, cirrhosis, smoking, and alcoholism), early blood transfusion and fresh frozen plasma (FFP) requirements, worst base deficit and blood gas pH in the first 12 hours, maximum 24-hour glucose, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), Acute Physiology and Chronic Health Evaluation II score, pulmonary artery catheter, and early steroid (<48 hours) requirements. Clinically relevant interaction terms were tested and kept in the final model if statistically significant ($p < 0.05$).

All data were summarized as mean \pm SD, median (interquartile range), or percentage. Student's *t* test or Mann-Whitney statistical test was used to compare continuous variables, whereas χ^2 or Fisher's exact test was used for categorical variables. The institutional review board of each participating center approved the cohort study, and the institutional review board at the University of Texas Southwestern Medical Center approved this current analysis.

RESULTS

Of the 1,036 patients in the entire trauma cohort, 921 survived beyond 48 hours from injury and constituted the study population. The overall mortality rate for this study cohort was 12.3%. These patients were significantly injured with a mean ISS of 31 ± 13 , with over 45% of patients receiving greater than 6 units of blood transfusion within the first 12 hours after injury and with 52% requiring an early (within 48 hours) exploratory laparotomy or thoracic surgical intervention.

As expected, patients who received EV therapy within the first 12 hours postinjury were older, more severely injured, had worse initial shock parameters, and required

Table 1 Comparison of Patients Who Did and Did Not Require Early Vasopressors Within 12 h Postinjury

	No EV (n = 802)	EV (n = 119)	p
Age (yr)	40.6 ± 18	46.8 ± 19	0.001*
Gender (%male)	64.2	71.4	0.123
Injury severity score	30.4 ± 13	34.1 ± 14	0.004*
ED GCS score	4.8 ± 4	5.0 ± 4	0.049*
Initial base deficit (meq/L)	8.5 ± 4	9.8 ± 5	0.003*
ED hypotension (SBP <90 mm Hg), %	62.4	79.8	0.001*
Blood transfusion (>6 units), %	42.8	63.9	0.001*
Fresh frozen plasma (12 h, mL)	1,001 ± 1,424	1,704 ± 1,934	0.001*
Early exploratory laparotomy (48 h), %	40.8	51.3	0.031*
Early thoracotomy/sternotomy (48 h), %	4.4	18.5	0.001*
Early steroid requirement (48 h), %	8.5	36.1	0.001*
Pulmonary artery catheter, %	20.6	53.8	0.001*
Length of stay (d)	23.1 ± 18	25.3 ± 22	0.231
ICU days	13.1 ± 12	18.9 ± 13	0.001*
Ventilator days	9.9 ± 11	15.9 ± 15	0.001*
Mortality, %	8.9	34.5	0.001*
Aggressive early crystalloid (>16 L), %	17.1	32.8	0.001*
APACHE II score, %	27.6	34.0	0.001*

* Statistically significant.

ED, emergency department; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 2 Comparison of Patients Who Did and Did Not Receive Aggressive Early Crystalloid Resuscitation (ECR >16 L) Within 12 h Postinjury

	ECR <16 L (n = 744)	ECR ≥16L (n = 177)	p
Age (yr)	41.9 ± 18	39.4 ± 18	0.091
Gender (%male)	63.2	73.3	0.011*
Injury severity score	29.9 ± 13	35.0 ± 13	0.001*
ED GCS score	8.9 ± 6	7.2 ± 5	0.001*
Initial base deficit (meq/L)	8.2 ± 4	10.7 ± 5	0.001*
ED hypotension (SBP <90 mm Hg), %	63.1	72.0	0.027*
Blood transfusion (>6 units), %	37.2	80.7	0.001*
Fresh frozen plasma (12 h, mL)	840 ± 1,274	2,165 ± 1,938	0.001*
Early exploratory laparotomy (48 h), %	36.6	66.5	0.001*
Early thoracotomy/sternotomy (48 h), %	5.0	11.4	0.002*
Early steroid requirement (48 h), %	10.6	18.2	0.001*
Pulmonary artery catheter, %	19.6	47.7	0.001*
Length of stay (d)	22.6 ± 19	26.7 ± 20	0.009*
ICU days	13.1 ± 13	16.8 ± 13	0.001*
Ventilator days	9.9 ± 11	13.5 ± 11	0.001*
Mortality, %	11.2	17.0	0.032*
Early vasopressor requirement (12 h)	10.8	22.2	0.001*
APACHE II score, %	27.5 ± 7	32.3 ± 6	0.001*

* Statistically significant.

ED, emergency department; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

greater resuscitation after injury (Table 1). They required greater intensive care unit and ventilator days, more often underwent pulmonary artery catheterization, and more commonly received aggressive ECR. Importantly, the crude mortality rate for those who received EV therapy was significantly higher than for those who did not (No EV 8.9% vs. EV 34.5%, $p = 0.001$). Similar findings are shown in Table 2, which compares patients who did and did not receive aggressive ECR within 12 hours postinjury. Those who received aggressive ECR also more commonly received EV

therapy. Again, those patients who received aggressive ECR also had a significantly higher crude mortality rate (No aggressive ECR 11.2% vs. aggressive ECR 17.0%, $p = 0.032$).

Our final hazard regression model was a good predictor of actual mortality with an area under the curve of 0.90 based on receiver operating characteristic analysis. This compared favorably to the receiver operating characteristic curve analysis of the Acute Physiology and Chronic Health Evaluation II score for all patients, which had an area under the curve of only 0.77. Because our two covariates of interest for this

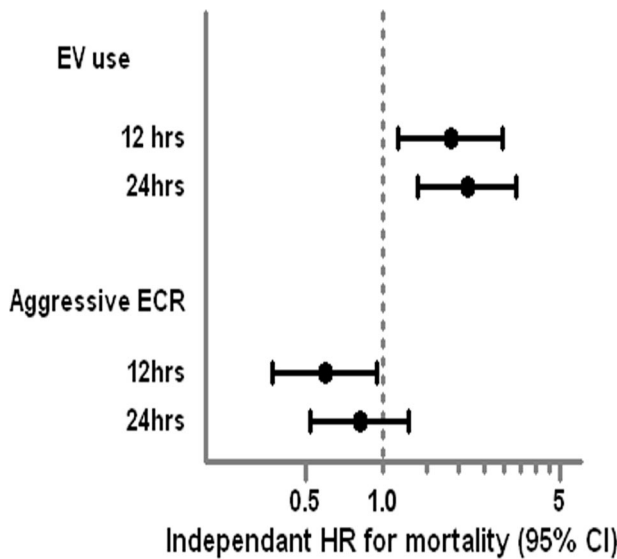


Fig. 2. Independent HRs for EV use and aggressive ECR at 12 and 24 hours postinjury. Additional covariates adjusted for in the model included age, gender, hospital center, ISS, ED pH, Glasgow Coma Scale score and base deficit, 12-hour blood and FFP requirements, comorbidities (hypertension, myocardial infarction, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, liver disease, smoking history, renal disease, alcoholism), hypotension on arrival, Acute Physiology and Chronic Health Evaluation II score, pulmonary artery catheter, early exploratory laparotomy, early thoracotomy/sternotomy, early steroid requirement, maximum 24-hour glucose, and interaction of age \times ISS.

analysis were to be placed into a single regression model, we appropriately tested for any statistical interaction between EV use and aggressive ECR. This interaction term was not significant ($p = 0.936$) and thus no interaction term was required in the final model.

Cox proportional hazard regression revealed that EV use within 12 hours after injury was independently associated with over an 80% higher risk of mortality (hazard ratio [HR] 1.81, 95% confidence interval [CI] 1.1–2.9, $p = 0.013$; Fig. 2). Within 24 hours from the time of injury, EV use was independently associated with over a twofold higher risk of mortality (HR 2.15, 95% CI 1.4–3.4, $p = 0.001$). In the same single regression model, aggressive ECR within 12 hours from injury was independently associated with a 40% reduction in mortality (HR 0.594, 95% CI 0.37–0.95, $p = 0.030$). The HR for aggressive ECR within 24 hours revealed a trend toward a survival advantage; however, this did not reach statistical significance (24-hour HR 0.81, 95% CI 0.52–1.3, $p = 0.364$). As both EV use and aggressive ECR were in the model simultaneously along with the other important confounders, their effect on the mortality risk is independent of each other. That is, independent of the amount of crystalloid resuscitation a patient received, EV use was associated with a higher mortality, and independent of EV use, aggressive ECR was found to be protective.

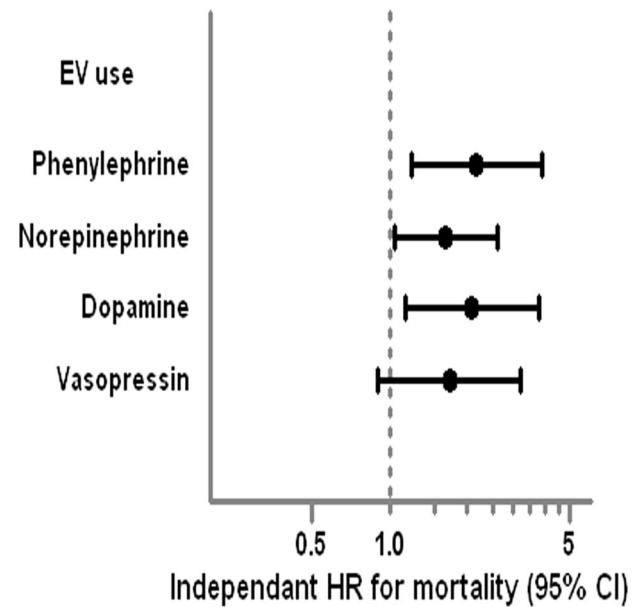


Fig. 3. Independent HRs for each vasopressor subtype. Additional covariates adjusted for in the model included aggressive ECR, age, hospital center, gender, ISS, ED pH, Glasgow Coma Scale score and base deficit, 12-hour blood and FFP requirements, comorbidities (hypertension, myocardial infarction, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, liver disease, smoking history, renal disease, alcoholism), hypotension on arrival, Acute Physiology and Chronic Health Evaluation II score, pulmonary artery catheter, early exploratory laparotomy, early thoracotomy/sternotomy, early steroid requirement, maximum 24-hour glucose, and interaction of age \times ISS.

When the model was stratified by age (≤ 55 years, $n = 730$ vs. > 55 years, $n = 191$), the risk of mortality for EV use within 24 hours remained unaltered (≤ 55 years, HR 2.0, 95% CI 1.1–3.6, $p = 0.019$ vs. > 55 years, HR 2.3, 95% CI 1.0–5.5, $p = 0.045$), indicating that neither older nor younger patients derived benefit from EV use. Interestingly, aggressive ECR within 12 hours was still found to be independently associated with a significant protective effect in the younger age group (≤ 55 years, HR 0.54, 95% CI 0.3–0.9, $p = 0.048$); however, based on interpretation of the HR, there was no protection afforded to those in the older age group (> 55 years, HR 1.08, 95% CI 0.4–2.8, $p = 0.875$). Finally, when individual vasopressor subtypes were placed into the model (Fig. 3), the detrimental effect on mortality remained consistent. Only the use of vasopressin was no longer statistically significant; however, the HR was 1.7, still depicting a higher risk for mortality.

DISCUSSION

Accumulating evidence has revealed that overly aggressive crystalloid resuscitation is associated with iatrogenic complications, thus renewing interest in use of vasopressors for early hemodynamic support for the injured patient. Inter-

estingly, Chernow et al.²⁹ has previously shown in primates that the innate sympathetic response to hemorrhage results in over a sixfold increase in baseline levels of endogenous norepinephrine and epinephrine within 15 minutes from hemorrhagic insult. They concluded that there is little justification for the use of exogenous catecholamines in hemorrhagic hypotension. Our findings from this analysis showed that, after controlling for important confounders, including early blood and plasma requirements, injury characteristics and early interventions, initial shock parameters, and preexisting medical conditions, EV use was independently associated with a higher risk of mortality, and this finding was consistent across all vasopressor subtypes analyzed. Additionally, the early use of aggressive crystalloid (>16 L) at 12 hours postinjury was a significant independent predictor of survival. These findings are unexpected and provide evidence that the early use of vasopressors for hemodynamic support may be deleterious, and should be used cautiously and not in place of aggressive crystalloid resuscitation after significant injury.

Patients who received EV therapy or aggressive ECR, as was demonstrated in this analysis, were more severely injured with greater physiologic derangements, more frequently requiring interventions and intensive care. Despite controlling for these confounders, EV use was still associated with almost a twofold higher mortality if used within 24 hours postinjury. Interestingly, despite having a higher crude mortality, patients who received aggressive ECR were statistically more likely to survive once these important confounders were controlled for. This finding was only significant at the 12-hour time point whereas the strength of the association was diluted at the 24-hour time point. This is physiologically intuitive as earlier correction of shock and organ perfusion has been shown to improve clinical outcome.^{30,31} Importantly, this association with reduced mortality seems to exist only with the younger patient population (age ≤ 55 years). Although aggressive ECR did not offer a protective effect in the older cohort, it was not associated with a higher mortality risk either.

This analysis is only a secondary data analysis and can only provide associations and does not prove causality. Therefore, patients who remain hypotensive despite aggressive resuscitation may require vasopressor support to maintain organ perfusion even early after injury and hemorrhagic shock. This analysis does suggest, however, that when vasopressors are used early, they should be used cautiously and only after aggressive crystalloid or colloid resuscitation has failed to maintain adequate tissue perfusion.

In the prehospital setting, it has been shown with penetrating torso trauma that delayed resuscitation improves overall survival.³² Delaying resuscitation allows for the attainment of surgical hemostasis before initiation of aggressive resuscitation. This current analysis focuses on the resuscitation period that occurs in concert with efforts to obtain hemostasis. Therefore, one should not extrapolate from these data that

they refute studies that demonstrate a potential benefit of permissive hypotension in the field.

The Inflammation and the Host Response to Injury, a large-scale collaborative program, represents a select cohort of significantly injured trauma patients with evidence of hemorrhagic shock.²⁴ It is in this group of patients in which our findings are most pertinent and applicable. It may be that in more elective postoperative surgical patients and other types of critically ill patients, minimization of crystalloid resuscitation and the early use of vasopressor therapy may provide benefit. Even in significantly injured patients, our findings are limited to the early resuscitation phase and the results of this study should not be generalized to the hemodynamic management outside this focal time period. It may be that minimization of crystalloid resuscitation and the use of vasopressors to provide hemodynamic support beyond this early time period improves outcome after injury, and further studies are required to decipher if this holds true.

This analysis has several potential limitations. First, this study is a secondary analysis of a prospective cohort study looking at the genomic and proteomic response after severe injury and hemorrhagic shock. As with any secondary analysis, data were not recorded to answer the specific hypothesis stated for this study. Potential confounding variables not able to be controlled for may be responsible for the associations described and the conclusions formulated in this analysis. EV use may be associated with such detrimental outcome that any statistical benefit is unable to be controlled for outside a randomized clinical trial. It is interesting, however, that we were able to find a statistical beneficial effect for aggressive ECR, which was also associated with much poorer outcome after unadjusted comparison alone. Despite our consistent findings across different vasopressor subtypes, it is likely that combinations of vasopressor therapy were used. This analysis was unable to control for which vasopressor was used first, nor did we control for any interaction for those patients for whom multiple vasopressors were required. Finally, as alluded to above, our results may not be reproducible or applicable in a less severely injured and more typical trauma population.

In conclusion, EV use within the first 24 hours after injury was independently associated with almost a twofold higher mortality, after controlling for all important confounders. Meanwhile, aggressive ECR was independently associated with a survival benefit. Although vasopressors may reduce fluid requirements and complications after the initial resuscitation, this analysis suggests that they should not be used early in the resuscitation phase. Instead, early hemodynamic support should rely primarily on aggressive crystalloid resuscitation in severely injured patients with hemorrhagic shock. Further prospective randomized studies are required to determine whether any benefit can be obtained from this practice soon after injury. Until this evidence exists, caution should be used for EV use within the first 24 hours after injury.

REFERENCES

- Cotton BA, Guy JS, Morris JA Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock*. 2006;26:115–121.
- Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238:641–648.
- Alam HB, Rhee P. New developments in fluid resuscitation. *Surg Clin North Am*. 2007;87:55–72, vi.
- Joshi GP. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth Analg*. 2005;101:601–605.
- Barak M, Rudin M, Vofsi O, Droyan A, Katz Y. Fluid administration during abdominal surgery influences on coagulation in the postoperative period. *Curr Surg*. 2004;61:459–462.
- Ng KF, Lam CC, Chan LC. In vivo effect of haemodilution with saline on coagulation: a randomized controlled trial. *Br J Anaesth*. 2002;88:475–480.
- Balogh Z, McKinley BA, Cocanour CS, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch Surg*. 2003;138:637–642, discussion 642–633.
- Bishop MH, Jorgens J, Shoemaker WC, et al. The relationship between ARDS, pulmonary infiltration, fluid balance, and hemodynamics in critically ill surgical patients. *Am Surg*. 1991; 57:785–792.
- Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis*. 1992; 145:990–998.
- Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet*. 2002;359:1812–1818.
- Christensen O. Mediation of cell volume regulation by Ca²⁺ influx through stretch-activated channels. *Nature*. 1987;330:66–68.
- Haussinger D, Schliess F, Warkulat U, vom Dahl S. Liver cell hydration. *Cell Biol Toxicol*. 1997;13:275–287.
- Haussinger D, Wettstein M, Warkulat U, vom Dahl S, Noe B, Schliess F. Cell volume signalling, osmolytes and liver function. *Digestion*. 1997;58(suppl 1):21–23.
- Lang F, Busch GL, Ritter M, et al. Functional significance of cell volume regulatory mechanisms. *Physiol Rev*. 1998;78:247–306.
- Watters JM, Tieu BH, Todd SR, et al. Fluid resuscitation increases inflammatory gene transcription after traumatic injury. *J Trauma*. 2006;61:300–308, discussion 308–309.
- Stern SA. Low-volume fluid resuscitation for presumed hemorrhagic shock: helpful or harmful? *Curr Opin Crit Care*. 2001;7:422–430.
- Feinstein AJ, Patel MB, Sanui M, Cohn SM, Majetschak M, Proctor KG. Resuscitation with pressors after traumatic brain injury. *J Am Coll Surg*. 2005;201:536–545.
- Sanui M, King DR, Feinstein AJ, Varon AJ, Cohn SM, Proctor KG. Effects of arginine vasopressin during resuscitation from hemorrhagic hypotension after traumatic brain injury. *Crit Care Med*. 2006;34:433–438.
- Feinstein AJ, Cohn SM, King DR, Sanui M, Proctor KG. Early vasopressin improves short-term survival after pulmonary contusion. *J Trauma*. 2005;59:876–882, discussion 882–883.
- Raedler C, Voelckel WG, Wenzel V, et al. Treatment of uncontrolled hemorrhagic shock after liver trauma: fatal effects of fluid resuscitation versus improved outcome after vasopressin. *Anesth Analg*. 2004;98:1759–1766, table of contents.
- Stadlbauer KH, Wagner-Berger HG, Raedler C, et al. Vasopressin, but not fluid resuscitation, enhances survival in a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. *Anesthesiology*. 2003;98:699–704.
- Voelckel WG, Raedler C, Wenzel V, et al. Arginine vasopressin, but not epinephrine, improves survival in uncontrolled hemorrhagic shock after liver trauma in pigs. *Crit Care Med*. 2003;31:1160–1165.
- Maier RV, Bankey P, McKinley B, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core—standard operating procedures for clinical care. Foreward. *J Trauma*. 2005;59:762–763.
- Moore FA, McKinley BA, Moore EE, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core—standard operating procedures for clinical care. III. Guidelines for shock resuscitation. *J Trauma*. 2006;61: 82–89.
- Minei JP, Nathens AB, West M, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core—standard operating procedures for clinical care. II. Guidelines for prevention, diagnosis and treatment of ventilator-associated pneumonia (VAP) in the trauma patient. *J Trauma*. 2006;60:1106–1113, discussion 1113.
- Nathens AB, Johnson JL, Minei JP, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core—standard operating procedures for clinical care. I. Guidelines for mechanical ventilation of the trauma patient. *J Trauma*. 2005;59:764–769.
- West MA, Shapiro MB, Nathens AB, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core—standard operating procedures for clinical care. IV. Guidelines for transfusion in the trauma patient. *J Trauma*. 2006;61:436–439.
- Brandt CA, Deshpande AM, Lu C, et al. TrialDB: a web-based clinical study data management system. *AMIA Annu Symp Proc*. 2003;2003:794.
- Chernow B, Lake CR, Barton M, et al. Sympathetic nervous system sensitivity to hemorrhagic hypotension in the subhuman primate. *J Trauma*. 1984;24:229–232.
- Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. *J Trauma*. 1993;35:584–588, discussion 588–589.
- Manikis P, Jankowski S, Zhang H, Kahn RJ, Vincent JL. Correlation of serial blood lactate levels to organ failure and mortality after trauma. *Am J Emerg Med*. 1995;13:619–622.
- Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331:1105–1109.