CORRESPONDENCE

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Immediate versus Delayed Fluid Resuscitation in Patients with Trauma

To the Editor: Dr. Bickell and his colleagues (Oct. 27 issue)[1] conclude that among hypotensive patients with penetrating injuries to the torso, "delay of aggressive fluid resuscitation until operative intervention improves the outcome." However, their data do not support this conclusion. First, the alternate-day selection method used to determine therapy is not a true technique of randomization. Second, the mortality in this study involves two groups of patients — those who died before they reached the operating room, most of whom had irreversible conditions, and those who died after surgery. When these groups were analyzed separately, there were no differences in the mortality rate. Preoperative death occurred in 41 of the 309 patients in the immediate-resuscitation group (13 percent) and in 29 of the 289 patients in the delayed-resuscitation group (10 percent, P = 0.25). Similarly, intraoperative or postoperative death occurred in 75 of the remaining 268 patients in the immediate-resuscitation group (28 percent) and in 57 of the remaining 260 patients in the delayed-resuscitation group (22 percent, P = 0.13). Neither difference is significant. When one considers also that the frequency of postoperative respiratory distress syndrome, sepsis, and other complications and the length of stay in the intensive care unit in the two groups were similar, one is forced to conclude that there was no difference between the two groups in outcome.

The total time from the arrival of paramedics on the scene to the patient's arrival at the trauma center was similar in the two groups, as was the time from arrival at the trauma center to surgery, but the intraoperative interval was significantly longer in the delayed-resuscitation group, which suggests that a longer intraoperative period of resuscitation was required. It seems likely that the relatively short time before surgery made the differences in fluid volume administered preoperatively physiologically unimportant and that the total volume of intraoperative crystalloid, blood, and blood products (which did not differ either in part or in the aggregate) does not in fact distinguish the two groups.

At the least, the evidence is insufficient to refute the many observations that adequate volume resuscitation is an effective mode of therapy as long as it does not delay surgical intervention.

John H. Siegel, M.D
New Jersey Trauma Center
Newark, NJ 07103-2406

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1. 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.[Free Full Text]

To the Editor: Bickell et al. fail to consider the effects of high-volume Ringer's solutions containing either acetate, which they used, or racemic d,l-lactate.[1,2] In addition to the time of fluid delivery, a major difference between groups

was that the immediate-resuscitation group received 2.5 liters of fluid containing 28 mmol of acetate per liter before surgery, whereas the delayed-resuscitation group received only 0.37 liter of fluid. The ability of acetate to cause adenosine release, hypotension, and vascular instability[3] could account for the lack of difference in blood pressure between the two groups just before surgery. In addition, when acetate is metabolized by the liver in the presence of catecholamines and vasopressin, as would be expected in shock, large amounts of calcium are sequestered in mitochondria, creating a pathologic picture similar to that observed in irreversible cell death. Acetate produces short-term increases in plasma concentrations of several cytokines in animals.[4] Therefore, in addition to dilution, acute cytokine-induced impairment of hepatic synthesis of clotting factors may account for the longer prothrombin and partial-thromboplastin times in the immediate-resuscitation group. The induction of fatal peritoneal fibrosis by acetate[5] has led to the discontinuation of its use in peritoneal dialysis fluids and strongly suggests that its use in resuscitation fluids is not without risk.

The principal alternative fluid used for resuscitation, Ringer's lactate, contains racemic d,l-lactate, which has neurologic toxic effects and can cause vascular collapse.[2] Furthermore, the routine use of uncharged hetastarch, which has 20 times less potency for plasma expansion than albumin, also shows that less toxic, more effective fluids are required if we are to improve outcomes in many standard treatments.

Although the authors are correct in raising questions about our routine treatment of trauma, before we accept their conclusion that rapid volume replacement in shock is harmful in itself, we must consider the possibility that the composition of the fluid, rather than the timing of fluid replacement, may cause increased mortality.

Richard L. Veech, M.D., D.Phil.
Tott's Gap Institute
Bangor, PA 18013

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To the Editor: Bickell et al. successfully conducted a difficult prospective study of the initial fluid treatment of patients with penetrating torso injuries, but we question their conclusion that aggressive fluid resuscitation should be delayed. First, the mean systolic blood pressure of 113 mm Hg among the patients in the delayed-resuscitation group on arrival in the operating room raises questions about the severity of the injuries. Fluid resuscitation may be a more important determinant of outcome in more severely injured patients. Second, the administration of 133 ml of packed red cells and 1608 ml of crystalloids in the immediate-resuscitation group for an average of 44 minutes between arrival in the trauma center and operation cannot be called aggressive therapy. Survival in that group might have been better had the patients received more fluid. Third, the mean interval before operation was short, making fluid resuscitation a less important determinant of outcome; the effect of fluid resuscitation might be different with longer preoperative intervals.

Martin R. Lessard, M.D.
Jacques G. Brochu, M.D.
Hôpital de l'Enfant-Jésus
Quebec, QC G3A 2H2, Canada

Jacques Brisson, M.D., D.Sc.
Hôpital du St. Sacrement
Quebec, QC G1S 4L8, Canada

To the Editor: It is surprising that in the study by Bickell et al., the mean systolic blood pressure in the delayed-resuscitation group increased without hemodynamic support from 59 mm Hg at the scene of injury to 113 mm Hg just before surgery, during an interval of 79 minutes. This suggests that the patients were not bleeding actively. This conclusion is consistent with the fact that the immediate-resuscitation group received only about 2500 ml of Ringer's acetate solution during this period. It is likely that some patients, although they were initially hypotensive, were not severely hypovolemic. Their initial hypotension may have been caused not by blood loss but by mobilization, tension pneumothorax, or cardiac tamponade.

The slight but substantial improvement in outcome in the delayed-resuscitation group may be questioned for several reasons. Twenty-two patients in this group inadvertently received rapid intravenous infusions. Were they the most severely injured of the group? Surgery was delayed for up to two hours in some patients in this group, suggesting that they were not severely injured. The authors make no distinction between deaths that occurred early (in the first 24 hours) and those that occurred late. On the one hand, delayed resuscitation may have decreased the number of late complications; on the other hand, it may have increased early death from exsanguination.

Precise analysis of the causes of early death in the 70 patients in both groups who died before surgery is necessary. These deaths may have been related to respiratory causes that are frequently misdiagnosed and not treated by paramedics in the prehospital setting.[1]

Considering the results of this study, it does not seem wise to change the traditional practice of prompt volume loading followed by rapid surgery in hypovolemic patients with trauma.

Pierre A. Carli, M.D.
Service d'Aide Médicale Urgente
75015 Paris, France

Jean E. de la Coussaye, M.D.
Centre Hospitalier Universitaire
30000 Nimes, France

Bruno Riou, M.D.
Centre Hospitalier Universitaire Pitié–Salpétrière
75013 Paris, France

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The authors reply:

To the Editor: Dr. Siegel notes that the alternate-day method we used to assign patients to treatment groups is not the conventional approach of most clinical trials. In the case of severely injured patients, however, formal randomization would have resulted in an unacceptable delay in the initiation of therapy. Dr. Siegel also suggests that we should have analyzed the preoperative and postoperative survival rates separately. We chose to focus this prospective study on survival to the time of hospital discharge as the primary outcome factor, rather than to conduct multiple analyses of intermediary steps of care.

In reply to Dr. Veech, there is no evidence that the composition of the various isotonic crystalloid solutions affects outcomes in patients with post-traumatic hypotension.[1]

Dr. Lessard et al. question the severity of injury in our patients because the mean systolic blood pressure in the delayed-resuscitation group at the time of their arrival in the operating room was 113 mm Hg. Before overinterpreting this finding, it is important to understand that only patients who survived to the time of operation were included in this group and that the patients, some with severe hypotension, who had died by this time were excluded from the study. Also, many patients received some fluid preoperatively according to protocol (i.e., a radiocontrast dye, antibiotic therapy, or limited intravenous infusion to maintain catheter patency). In addition, some spontaneous recovery after hemorrhagic hypotension is a well-described phenomenon in both experimental and clinical practice settings.[2] The suggestion that fluid resuscitation may be more important in patients with more severe injuries prompted us to examine our data further. When the analysis was limited to patients with Injury Severity Scores of 25 or higher, the findings were even more striking; the survival rates were 48 percent in the immediate-resuscitation group and 61 percent in the delayed-resuscitation group ($P = 0.02$).

We agree with the comment of Dr. Carli et al. that some of the hypotensive injury victims in this study were not necessarily hypovolemic to the point of hemorrhagic shock. For that reason, we avoided the term hemorrhagic shock in favor of the term post-traumatic hypotension. The 22 patients assigned to the delayed-resuscitation group who received intravenous fluid infusions in violation of the protocol did not differ from the other patients in that group with respect to their Revised Trauma Scores, Injury Severity Scores, or probability of survival. These 22 patients were not excluded because the analyses were conducted on an intention-to-treat basis.

If anything, this potential study bias resulted in a smaller difference between the two study groups.[3] We agree with Carli et al. that the ventilatory status of patients with unstable injuries is an important consideration. We conducted a detailed review of the clinical records and autopsy reports of all patients who died in this study. Of the 70 who died before surgery, all were intubated and received mechanical ventilation in a timely fashion, and we found no cases of undiagnosed respiratory failure or esophageal intubation.

William H. Bickell, M.D.
St. Francis Hospital
Tulsa, OK 74136

Paul E. Pepe, M.D.
City of Houston Emergency Medical Services
Houston, TX 77002

Kenneth L. Mattox, M.D.
Baylor College of Medicine
Houston, TX 77030

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