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## IMMEDIATE VERSUS DELAYED FLUID RESUSCITATION FOR HYPOTENSIVE PATIENTS WITH PENETRATING TORSO INJURIES

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**Abstract Background.** Fluid resuscitation may be detrimental when given before bleeding is controlled in patients with trauma. The purpose of this study was to determine the effects of delaying fluid resuscitation until the time of operative intervention in hypotensive patients with penetrating injuries to the torso.

**Methods.** We conducted a prospective trial comparing immediate and delayed fluid resuscitation in 598 adults with penetrating torso injuries who presented with a pre-hospital systolic blood pressure  $\leq 90$  mm Hg. The study setting was a city with a single centralized system of pre-hospital emergency care and a single receiving facility for patients with major trauma. Patients assigned to the immediate-resuscitation group received standard fluid resuscitation before they reached the hospital and in the trauma center, and those assigned to the delayed-resuscitation group received intravenous cannulation but no fluid resuscitation until they reached the operating room.

FOR the past two decades the preoperative approach to hypotensive patients with trauma in North America has included prompt intravenous infusion of isotonic fluids.<sup>1-3</sup> The rationale for this treatment has been to sustain tissue perfusion and vital organ function while diagnostic and therapeutic procedures are performed. This approach was based largely on the demonstration in animals in the 1950s and 1960s<sup>4-6</sup> that isotonic-fluid resuscitation was an important life-sparing component of therapy for severe hypotension due to hemorrhage.<sup>4-6</sup> If perfusion of vital organs was rapidly restored by the intravenous administration of blood, crystalloids, or both, the animals generally survived, whereas untreated animals died or had irreversible organ damage due to ischemia.

On the other hand, others have expressed concern that intravenous volume infusion may be detrimental in the clinical setting if administered before the hem-

**Results.** Among the 289 patients who received delayed fluid resuscitation, 203 (70 percent) survived and were discharged from the hospital, as compared with 193 of the 309 patients (62 percent) who received immediate fluid resuscitation ( $P = 0.04$ ). The mean estimated intraoperative blood loss was similar in the two groups. Among the 238 patients in the delayed-resuscitation group who survived to the postoperative period, 55 (23 percent) had one or more complications (adult respiratory distress syndrome, sepsis syndrome, acute renal failure, coagulopathy, wound infection, and pneumonia), as compared with 69 of the 227 patients (30 percent) in the immediate-resuscitation group ( $P = 0.08$ ). The duration of hospitalization was shorter in the delayed-resuscitation group.

**Conclusions.** For hypotensive patients with penetrating torso injuries, delay of aggressive fluid resuscitation until operative intervention improves the outcome. (N Engl J Med 1994;331:1105-9.)

orrhage is surgically controlled.<sup>7-13</sup> More recent studies have demonstrated that in uncontrolled hemorrhage, aggressive administration of fluids may disrupt the formation of thrombus, increase bleeding, and decrease survival.<sup>14-18</sup>

The objective of this study was to test the hypothesis that the survival of hypotensive patients with penetrating injuries to the torso would be improved if fluid resuscitation was restricted until the time of operative intervention. We also determined the effect of delayed fluid resuscitation on intraoperative hemorrhage, the length of hospitalization, and the frequency of postoperative complications.

## METHODS

### Study Subjects

Patients eligible for this study were adults or adolescents (age,  $\geq 16$  years) with gunshot or stab wounds to the torso who had a systolic blood pressure  $\leq 90$  mm Hg, including patients with no measurable blood pressure, at the time of the initial on-scene assessment by paramedics from the City of Houston Emergency Medical Services system.<sup>19</sup> The torso was delineated superiorly by the upper end of the neck, anteroinferiorly by the inguinal ligaments and symphysis pubis, and posteroinferiorly by the gluteal folds. Pregnant women were not enrolled in the study. All patients within the city limits of Houston who met the entry criteria were transported directly by ground ambulance to the city's only receiving facility for patients with major trauma, Ben Taub General Hospital.

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Patients included in the final study analysis were those in whom fluid resuscitation might affect outcome. Part of the prospective study design was to exclude the following from the outcome analysis: patients with a Revised Trauma Score of zero at the scene of the injury, those who also had a fatal gunshot wound to the head, and patients with minor injuries not requiring operative intervention. The paramedics caring for the patients were not aware of these exclusion criteria and treated all hypotensive patients with penetrating torso injuries according to the protocol.

### Human-Subjects Review

A policy of waived consent, which adhered to the principle of implied consent, was approved by the institutional review board of Baylor College of Medicine, the Harris County Hospital District, and the City of Houston Emergency Medical Services.<sup>20,21</sup> This waiver of informed consent followed the guidelines specified by federal regulation.<sup>22</sup>

### Setting

The city of Houston has a population of approximately 2 million. The Houston Fire Department is the sole provider of prehospital emergency medical care within the city limits.<sup>19,23</sup> The Ben Taub Trauma Center and the emergency medical system are staffed by members of the faculty and house staff of the Department of Surgery at Baylor College of Medicine.

### Study Interventions

All patients enrolled in the study were assigned to one of two groups: the immediate-resuscitation group, in which intravascular fluid resuscitation was given before surgical intervention in both the prehospital and trauma-center settings, or the delayed-resuscitation group, in which intravenous fluid resuscitation was delayed until operative intervention. The operative interventions included thoracotomy at the trauma center, thoracotomy in the operating room, laparotomy, neck exploration, and groin exploration. Patients injured on even-numbered days of the month were enrolled in the immediate-resuscitation group, whereas those injured on odd-numbered days were enrolled in the delayed-resuscitation group. The alternating 24-hour periods corresponded to the 24-hour shifts worked by both the paramedics and the trauma teams. Because there were three rotating teams of paramedics and surgical house staff, assignments to the groups were alternated automatically for both prehospital and hospital staff members. Under the specific circumstances being studied, formal randomization procedures were considered not to be logistically feasible. The alternate-day assignment endorsed by the institutional review board prospectively sets a treatment plan for each patient and thus avoids detrimental delays in care for critically injured patients. Except for the preoperative-fluid variable, all other treatment protocols were identical for the two study groups.

### Study Protocol

During the prehospital phase, patients assigned to receive immediate fluid resuscitation were treated with a standard paramedical protocol<sup>1-3</sup> that included endotracheal intubation and assisted ventilation with oxygen when appropriate, rapid transport to the emergency center, and insertion of two or more 14-gauge intravenous catheters in the upper extremities for rapid infusion of isotonic crystalloid (Ringer's acetate solution) en route to the hospital. In accordance with recent recommendations, no patients were treated with antishock garments.<sup>24</sup> Patients with a systolic blood pressure below 100 mm Hg (as determined by auscultation) on arrival at the emergency center received continued intravenous infusions of crystalloid. When necessary, packed red cells were infused according to standard criteria established by the American College of Surgeons Committee on Trauma.<sup>25</sup> Patients assigned to the delayed-resuscitation group were cared for in an identical manner with the exception that after the insertion of the intravenous catheters, the catheter lumens were covered with an infusion cap that was then flushed with 1 to 2 ml of 1 percent heparin in normal saline. Any additional peripheral or central venous catheters inserted at the emergency center were kept patent by the infusion of Ringer's acetate solution at a rate of 10 ml per hour. After a patient arrived in the operating

room and was placed under general anesthesia, intravenous crystalloid and packed red cells were given as needed, regardless of study-group assignment, to maintain systolic arterial pressure of 100 mm Hg, hematocrit  $\geq$  25 percent, and urinary output  $\geq$  50 ml per hour.<sup>25</sup> Hetastarch was occasionally given as an additional intravascular volume expander.

### Main Measurements and Secondary Outcome Variables

The components of the Revised Trauma Score were determined immediately by paramedics at the scene and at the trauma center by surgical house staff.<sup>26</sup> The times at which emergency vehicles were dispatched, arrived at the scene, departed from the scene, and arrived at the trauma center were recorded by a computerized dispatch system.<sup>23</sup> For the purpose of this study, the response interval was defined as the length of time between the first telephone ring at the public-safety answering point (911 center) and the arrival of the ambulance at the street location.<sup>19,23</sup> The scene interval was defined as the time between the arrival of the ambulance and its departure from that location. The transport interval was defined as the time between the departure from the scene and ambulance docking at the trauma center. The trauma-center interval was defined as the time from the patient's arrival at the center until the patient was transported to the operating room (not the preoperative holding area).

Both the 1985 and 1990 versions of the Abbreviated Injury Scale were used to determine scores retrospectively for each patient on the basis of a physical examination, a chart review, operative reports, and autopsy results.<sup>27,28</sup> A score of 6 on the Abbreviated Injury Scale was considered to indicate a fatal head injury. The probability of survival was calculated from the age, cause of injury, Revised Trauma Score, and Injury Severity Score with the use of established criteria.<sup>26,27</sup> The Revised Trauma Score uses three physiologic measures to quantitate the physiologic severity of injury: the Glasgow Coma Scale, systolic blood pressure, and respiratory rate. The Revised Trauma Score ranges from 0 (full cardiopulmonary arrest) to 7.84 (a respiratory rate of 10 to 29 per minute, systolic blood pressure of more than 89 mm Hg, and a score on the Glasgow Coma scale of 13 to 15). The Abbreviated Injury Scale is a numerical scoring system for rating organ damage sustained during trauma. The Injury Severity Score (mathematically derived from the Abbreviated Injury Scale) ranges from 1 (an extremely minor injury) to 75 (generally a fatal injury). Blood pressures were measured in the trauma center by nurses who were not part of the study team. Survivors were defined as patients who did not die during hospitalization.

Patients surviving after operation were assessed for six prospectively defined postoperative complications: wound infection, adult respiratory distress syndrome, sepsis syndrome, acute renal failure, coagulopathy, and pneumonia.<sup>29-31</sup>

### Statistical Analysis

The a priori sample size was calculated on the assumption that death would occur in 35 percent of patients receiving standard preoperative fluid resuscitation for penetrating torso injuries. On the basis of experimental data and previous clinical experience, an estimated 10 to 15 percent improvement in survival was predicted if fluid resuscitation was delayed until operative intervention.<sup>15,17,24</sup> With a two-tailed alpha value of 0.05 and a beta value of 0.2, it was determined that the study should continue until approximately 600 patients were enrolled.

Analyses were made on an intention-to-treat basis. Categorical variables were compared with chi-square tests, and continuous variables were compared with the Mann-Whitney U rank-sum test. Continuous variables are expressed as means  $\pm$  SD. All P values are two-tailed. The results presented are the final results of a 37-month investigation with one interim analysis.<sup>31</sup> For the final analysis, all P values of less than 0.05 were considered to indicate statistical significance according to the Haybittle-Peto boundary.<sup>32</sup>

## RESULTS

### Characteristics of the Patients

During the 37-month study (November 1, 1989, to December 22, 1992), a total of 1069 consecutive pa-

tients with hypotension and penetrating injuries to the torso were transported by the Houston Emergency Medical Services system to Ben Taub General Hospital. Of the 1069 patients, 172 (16 percent) had a Revised Trauma Score of zero on initial evaluation by paramedics. Another 299 patients (28 percent) subsequently were found to have minor injuries that did not require thoracotomy, laparotomy, or neck or groin exploration. The numbers of patients with these exclusion factors in each group were very similar.

Among the remaining 598 patients, 309 were enrolled in the immediate-resuscitation group and 289 in the delayed-resuscitation group. The two study groups were well matched in terms of demographic and clinical characteristics (Table 1). Prehospital administration of Ringer's acetate solution was associated with a significant increase in systolic arterial blood pressure by the time of arrival at the emergency center. The initial hemoglobin concentration and platelet count were significantly lower in the immediate-resuscitation group, whereas the prothrombin and partial-thromboplastin times were longer (Table 2). However, there were no significant differences between the two groups with respect to the systemic arterial pH or venous serum bicarbonate concentration.

Of the 598 patients, 70 patients died before they reached the operating room and 528 underwent operative intervention — 268 in the immediate-resuscitation group (87 percent) and 260 in the delayed-resuscitation group (90 percent). On arrival in the operating room and before the induction of anesthesia, the groups were similar with respect to systolic and diastolic blood pressures, pH, and venous bicarbonate concentrations (Table 3). However, as was true for values recorded on arrival at the trauma center, the mean hemoglobin concentration was significantly lower in the immediate-resuscitation group (Table 3).

#### Fluid Volumes Administered

During the prehospital phase of patient care, the volume of Ringer's acetate solution administered in the immediate-resuscitation group averaged 870 ml, as compared with 92 ml in the delayed-resuscitation group (Table 4). The volumes administered at the trauma center averaged 1608 ml and 283 ml, respectively. The administration of antibiotics and contrast medium as well as the placement of additional intravenous catheters (kept at a minimal flow rate to maintain patency) resulted in the infusion of small volumes of fluid in the delayed-resuscitation group. Rapid intravenous infusions of fluid were initiated inadvertently in 10 patients (4 percent) in the delayed-resuscitation group but were discontinued during the trip to the hospital. In 12 other patients assigned to the delayed-resuscitation group (4 percent), rapid infusions of fluid were transiently administered at the trauma center in violation of the protocol. Except for these 22 patients, fluid was restricted in all patients in the delayed-resuscitation group until their arrival in the operating room, regardless of their clinical condition.

Among the 528 patients who underwent operation, there was no significant difference in the volume of

**Table 1. Characteristics of 598 Patients with Penetrating Torso Injuries Who Received Immediate or Delayed Fluid Resuscitation.\***

CHARACTERISTIC	IMMEDIATE RESUSCITATION (N = 309)	DELAYED RESUSCITATION (N = 289)
Age (yr)	31 ± 11	31 ± 10
Male sex (% of patients)	88	91
Systolic blood pressure (mm Hg)	58 ± 35	59 ± 34
Injury Severity Score	26 ± 14	26 ± 14
Revised Trauma Score	5.4 ± 2.1	5.6 ± 2.1
Probability of survival	69	72
Mechanism of injury (% of patients)		
Gunshot wound	65	67
Stab wound	29	30
Shotgun-blast wound	6	3
Primary site of surface injury (% of patients)		
Neck	5	3
Chest	33	35
Abdomen	63	62
Patient care times (min)		
Response interval	8 ± 5	8 ± 6
Scene interval	9 ± 8	7 ± 6
Transport interval	13 ± 6	12 ± 6
Trauma-center interval	44 ± 65	52 ± 99
Intraoperative interval	114 ± 105	134 ± 101†

\*Plus-minus values are means ± SD.

†P = 0.028 for the comparison between groups.

Ringer's acetate or hetastarch administered to the two groups during surgery (Table 4). In addition, the patients in both groups received similar amounts of packed red cells, fresh-frozen plasma, platelets, and autologous blood transfusions. However, the mean (±SD) rate of fluid administration (delivered in an attempt to maintain a systolic blood pressure of 100 mm Hg) was significantly higher in the immediate-resuscitation group than in the delayed-resuscitation group (117 ± 126 ml per minute vs. 91 ± 80 ml per minute, P = 0.008).

#### Outcome and Complications

The overall rate of survival was significantly higher in the delayed-resuscitation group than in the immediate-resuscitation group (70 percent vs. 62 percent, P = 0.04) (Table 5). The difference in survival was not altered after adjustment for the prehospital and trauma-center intervals. There was a trend toward increased intraoperative blood loss in the immediate-

**Table 2. Systemic Arterial Blood Pressure and Laboratory Findings on Arrival at the Trauma Center in Patients with Penetrating Torso Injuries, According to Treatment Group.\***

VARIABLE	IMMEDIATE RESUSCITATION (N = 309)	DELAYED RESUSCITATION (N = 289)	P VALUE
Systolic blood pressure (mm Hg)	79 ± 46	72 ± 43	0.02
Hemoglobin (g/dl)	11.2 ± 2.6	12.9 ± 2.2	<0.001
Platelet count (× 10 <sup>-3</sup> /mm <sup>3</sup> )	274 ± 84	297 ± 88	0.004
Prothrombin time (sec)	14.1 ± 16	11.4 ± 1.8	<0.001
Partial-thromboplastin time (sec)	31.8 ± 19.3	27.5 ± 12	0.007
Systemic arterial pH	7.29 ± 0.17	7.28 ± 0.15	0.46
Serum bicarbonate concentration (mmol/liter)	20 ± 10	20 ± 11	0.82

\*Plus-minus values are means ± SD. To convert values for hemoglobin to millimoles per liter, multiply by 0.62.

**Table 3. Systemic Arterial Blood Pressure, Heart Rate, and Laboratory Findings at the Time of Initial Operative Intervention in Patients with Penetrating Torso Injuries, According to Treatment Group.\***

VARIABLE	IMMEDIATE RESUSCITATION (N = 268)	DELAYED RESUSCITATION (N = 260)	P VALUE
Systolic blood pressure (mm Hg)	112±33	113±30	0.98
Diastolic blood pressure (mm Hg)	57±22	60±21	0.10
Heart rate (beats/min)	102±25	104±23	0.25
Hemoglobin (g/dl)	10.7±5.8	11.5±2.6	<0.001
Platelet count (×10 <sup>-3</sup> /mm <sup>3</sup> )	195±97	198±105	0.99
Systemic arterial pH	7.27±0.16	7.28±0.15	0.75
Serum bicarbonate concentration (mmol/liter)	21±5	20±4	0.39

\*Plus-minus values are means ±SD. To convert values for hemoglobin to millimoles per liter, multiply by 0.62.

resuscitation group (P = 0.11). The patients in the immediate-resuscitation group had significantly longer total hospital stays, but the length of stay in the intensive care unit did not differ significantly between the two groups.

As expected, all patients excluded from the outcome analysis because of an initial prehospital Revised Trauma Score of zero died. Conversely, all patients subsequently excluded from the analyses because they did not require operative interventions survived.

The frequency of complications in each group was similar (Table 6). However, there was a trend toward more complications in the immediate-resuscitation group (P = 0.08).

## DISCUSSION

Our study shows that aggressive administration of intravenous fluids to hypotensive patients with penetrating injuries to the torso should be delayed until the time of operative intervention. Evolving studies in animals have provided the probable explanation for a detrimental effect of preoperative fluid adminis-

**Table 4. Total Volumes of Fluids Administered to Patients with Penetrating Torso Injuries, According to Treatment Group.\***

VARIABLE	IMMEDIATE RESUSCITATION (N = 309)	DELAYED RESUSCITATION (N = 289)	P VALUE
Before arrival at the hospital			
Ringer's acetate (ml)	870±667	92±309	<0.001
Trauma center			
Ringer's acetate (ml)	1608±1201	283±722	<0.001
Packed red cells (ml)	133±393	11±88	<0.001
Operating room†			
Ringer's acetate (ml)	6772±4688	6529±4863	0.31
Packed red cells (ml)	1942±2322	1713±2313	0.07
Fresh-frozen plasma or platelet packs (ml)	357±1002	307±704	0.45
Autologous-transfusion volume (ml)	95±486	111±690	0.76
Hetastarch (ml)	499±717	542±696	0.41
Rate of intraoperative fluid administration (ml/min)	117±126	91±88	0.008

\*Plus-minus values are means ±SD.

†For these analyses there were 268 patients in the immediate-resuscitation group and 260 patients in the delayed-resuscitation group.

tration.<sup>14-18,33-37</sup> Specifically, fluids given before surgical control of bleeding lead to either accentuation of ongoing hemorrhage or hydraulic disruption of an effective thrombus, followed by a fatal secondary hemorrhage.<sup>34</sup> In addition, intravenous infusions of crystalloid may promote hemorrhage by diluting coagulation factors<sup>17</sup> and by lowering blood viscosity, thereby decreasing the resistance to flow around an incomplete thrombus.<sup>36</sup>

The mechanism of the detrimental effect of fluid administration in humans is difficult to ascertain. In our study, a trend toward more intraoperative blood loss was found in the immediate-resuscitation group, but the volume of blood loss could not be measured in the more applicable prehospital and trauma-center phases of management, when control of internal hemorrhage was not attempted.

Nonetheless, other clinical findings are consistent with the hypotheses derived from experiments in animals. The initial mean systolic blood pressure measured at the emergency center was significantly higher in the immediate-resuscitation group. Also, despite the relatively small amount of crystalloid infused in

**Table 5. Outcome of Patients with Penetrating Torso Injuries, According to Treatment Group.**

VARIABLE	IMMEDIATE RESUSCITATION	DELAYED RESUSCITATION	P VALUE
Survival to discharge — no. of patients/total patients (%)	193/309 (62)*	203/289 (70)†	0.04
Estimated intraoperative blood loss — ml‡	3127±4937	2555±3546	0.11
Length of hospital stay — days§	14±24	11±19	0.006
Length of ICU stay — days§	8±16	7±11	0.30

\*95 percent confidence interval, 57 to 68 percent.

†95 percent confidence interval, 65 to 75 percent.

‡The estimated intraoperative blood loss was calculated for patients who survived the operation: 268 in the immediate-resuscitation group and 260 in the delayed-resuscitation group.

§The lengths of stays in the hospital and intensive care unit (ICU) were calculated for patients who survived the operation: 227 in the immediate-resuscitation group and 238 in the delayed-resuscitation group.

the prehospital setting, the mean hemoglobin concentration at the emergency center was lower in the immediate-resuscitation group, suggesting accentuated bleeding and not just an associated effect of hemodilution. Similarly, the prothrombin and partial-thromboplastin times were more prolonged in this group. Although these clinical associations of elevated blood pressure, relative hemodilution, and longer clotting times for the group in which the survival rate was lower (the immediate-resuscitation group) do not prove the proposed hypotheses, the findings are compatible with the postulated mechanisms for accentuated or secondary hemorrhage.

Some data have suggested that limited administration of fluids with the use of an extremely low blood-pressure level as an end point (e.g., 40 mm Hg) may help maintain limited tissue perfusion in severely hypotensive animals without the adverse effects of accelerated hemorrhage and the associated increased risk

**Table 6. Postoperative Complications in Patients with Penetrating Torso Injuries, According to Treatment Group.\***

COMPLICATION	IMMEDIATE RESUSCITATION		DELAYED RESUSCITATION		P VALUE
	NO. OF PATIENTS	PERCENT (95% CI)	NO. OF PATIENTS	PERCENT (95% CI)	
Adult respiratory distress syndrome	8	4 (2-6)	3	1 (0-3)	0.11
Sepsis syndrome	12	5 (3-9)	11	5 (3-8)	0.74
Acute renal failure	8	4 (2-6)	3	1 (0-3)	0.11
Coagulopathy	24	11 (7-15)	19	8 (5-12)	0.34
Wound infection	21	9 (9-17)	24	10 (7-14)	0.36
Pneumonia	28	12 (9-17)	22	9 (6-13)	0.28
Patients with $\geq 1$ complications	69	30 (25-36)	55	23 (18-29)	0.08

\*Several patients had more than one complication. CI denotes confidence interval.

of death.<sup>18,37</sup> However, patients in this study who had systemic arterial blood pressures below 40 mm Hg were generally pulseless and clinically moribund, so that their chances of survival were small, regardless of treatment. Therefore, statistically sound evidence for infusing fluids in this small cohort of patients is still lacking.

Our results challenge traditional practices that espouse aggressive and universal preoperative intravenous infusion of fluids for patients with trauma and hypotension of presumed hemorrhagic origin.<sup>1-3</sup> Although this study of preoperative fluid resuscitation for hypotensive patients with trauma does not necessarily refute the classic studies cited previously,<sup>4-6</sup> it refutes the broad interpretation and extrapolation of those experiments to all aspects of management of trauma. It is not the value of fluid resuscitation that is currently being debated, but rather the volume, timing, and extent of that resuscitation for certain patients. Although the study results should not be directly extrapolated to all age groups, to hypotensive patients with blunt trauma or severe head injuries, or to the rural trauma care setting, they do suggest the consideration of similar studies in these groups of patients.

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