

## PRELIMINARY REPORTS

### Out-of-hospital Administration of Mannitol to Head-injured Patients Does Not Change Systolic Blood Pressure

Michael R. Sayre, MD, Stephen W. Daily, MD, Susan A. Stern, MD, Daniel L. Storer, MD, Harry R. van Loveren, MD, James M. Hurst, MD

#### ABSTRACT

**Objective:** To determine the effect of out-of-hospital mannitol administration on systolic blood pressure (BP) in the head-injured multiple-trauma patient.

**Methods:** This was a prospective, randomized, double-blind, placebo-controlled clinical trial involving a university-based helicopter air medical service and level-1 trauma center hospital. Endotracheally intubated head-trauma victims with Glasgow Coma Scale (GCS) scores < 12 were enrolled from November 22, 1991, to November 20, 1992, if evaluated by the participating aeromedical transport team within 6 hours of injury. Patients were excluded if they were <18 years old, had already received mannitol or another diuretic, were potentially pregnant, or were receiving CPR. All patients were intubated prior to study drug (mannitol [1 g/kg] or normal saline) use. Pulse and BP were measured every 15 minutes for 2 hours following study drug administration.

**Results:** A total of 44 patients were enrolled. After exclusion of 3 patients who did not meet all inclusion criteria, there were 20 patients in the mannitol group and 21 patients in the placebo group. The groups were similar at baseline in age, pulse, systolic BP (baseline mannitol:  $124 \pm 47$  mm Hg; placebo:  $128 \pm 32$  mm Hg), GCS score, and Injury Severity Scale score. Systolic BP did not change significantly throughout the observation period in either group. This study had 83% power to detect a mean systolic BP drop to <90 mm Hg.

**Conclusion:** Out-of-hospital administration of mannitol did not significantly change systolic BP in this group of head-injured multiple-trauma patients.

**Key words:** head injury; brain injury; mannitol; emergency medical services; patient transport; hemodynamics—blood pressure.

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■ The most common cause of death in the United States among persons aged 1–44 years is injury. Approximately 50% of all trauma deaths are due to head injury,<sup>1</sup> and there are about 19 head-injury deaths an-

nually per 100,000 U.S. residents.<sup>2</sup> At the present time, the optimal treatment for severe head injury is unknown.

One of the mechanisms for the high morbidity and mortality associated with head injury is a rise in intra-

*From the University of Cincinnati Medical Center, Cincinnati, OH, Department of Emergency Medicine (MRS, SWD, DLS), Department of Neurosurgery (HRvL), and Department of Surgery (JMH), and the University of Michigan, Ann Arbor, MI, Department of Surgery, Section of Emergency Medicine (SAS).*

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*Address for correspondence and reprints: Michael R. Sayre, MD, Department of Emergency Medicine, University of Cincinnati Medical Center, 231 Bethesda Avenue, Cincinnati, OH 45267-0769. Fax: 513-558-5791; e-mail: michael.sayre@oa.uc.edu*

cranial pressure (ICP) with subsequent neuronal ischemia. Published recommendations for the management of elevated ICP include endotracheal intubation and hyperventilation followed by IV administration of mannitol only when elevated ICP is proven or strongly suspected.<sup>3,4</sup> However, some physicians are concerned about possible hemodynamic instability, which might result from the osmotic diuresis following mannitol administration in a multiple-trauma patient.<sup>5</sup> Based on this concern, some trauma systems discourage the use of mannitol prior to volume resuscitation and stabilization of the patient. There are few data to support the recommendation to withhold mannitol, and this approach may deprive head-injured patients of beneficial therapy.<sup>6-8</sup> Previous studies involving mannitol administration have been conducted in the intensive care unit (ICU), operating theater, and ED. Little work has focused on the use of mannitol before hospital arrival.

The purpose of this study was to assess the safety of mannitol administration to the head-injured multiple-trauma patient in the out-of-hospital emergency care setting. We hypothesized that early administration of mannitol in the out-of-hospital setting would have no effect on the systolic blood pressures (BPs) of head-injured multiple-trauma patients.

## METHODS

### Study Design

This was a prospective, randomized, double-blind, placebo-controlled clinical trial of the effect of mannitol on systolic BP in multiply injured patients with severe head injuries. The research protocol was approved by the University of Cincinnati Institutional Review Board (IRB), with a waiver of prospective informed consent. If they were available, the patient's family were apprised of the study as soon as possible after hospital arrival.

### Setting and Participants

Specific trauma patients who were being transported by a university hospital-based helicopter air medical service to that hospital's level-1 trauma center from November 22, 1991, through November 20, 1992, were considered for enrollment. The air medical service transports approximately 625 trauma patients per year. Eligibility for entry into the study was determined by the flight crew. The flight team consisted of an experienced flight nurse and an emergency medicine (EM) resident physician. The flight crew was able to perform endotracheal intubation followed by hyperventilation with a portable ventilator after loading the patient into the aircraft. In addition, the medical team carried non-cross-matched blood for administration to patients with hemorrhagic shock.

Head-injured patients were eligible for inclusion if they had a Glasgow Coma Scale (GCS) score < 12, had IV access, had airway control with an endotracheal tube, and were being hyperventilated. In addition, they had to be entered into the study within 6 hours of injury.

Patients were excluded if they were <18 years old, had received mannitol or another diuretic since the time of the traumatic incident, or were undergoing CPR. At the request of the IRB, women <50 years old were excluded, unless their medical records clearly documented a previous tubal ligation or hysterectomy.

### Experimental Protocol

As soon as possible after intubation and stabilization of the patient's airway and breathing, the study solution was administered. Patients were randomized to either control or treatment groups by block randomization. The control group received 5 mL/kg of 0.9% saline solution (308 mOsmol/L), while the treatment group received 5 mL/kg of 20% mannitol (1,098 mOsmol/L). The latter volume of solution provides a dose of 1 g/kg of mannitol. The study solution was administered as rapidly as possible through a blood filter into a large-bore IV catheter. The flight crew was instructed to pump the solution into the patient so that it would be administered over as little as 5 minutes.<sup>9</sup> No additional mannitol or other diuretic was administered during the remainder of the transport.

The study solutions were prepared by the pharmacy department and were identified by a code number. An envelope showing the code number identified the contents of that IV bag. If the treating physicians at the receiving trauma center believed it was necessary to know whether the patient had received mannitol or placebo, the envelope could be opened.

### Measurements

Data were collected just prior to and immediately after administration of head injury solution, at least every 15 minutes during transport, upon arrival in the ED, and every 15 minutes thereafter for 2 hours. Each data set included time of day, systolic and diastolic BPs, heart rate, respiratory rate, airway status (controlled or spontaneous respirations), IV solution(s) being infused, volume infused, and flow rate. In addition, GCS scores were obtained on initial patient contact, upon arrival in the ED, and at the end of the 2-hour study period. All the patients received Foley catheters, and urine outputs were recorded with the ED data sets. At the end of the 2-hour observation period, the results of arterial blood gases (ABGs), electrolytes, and CT scans were recorded. The presence or absence of inflated pneumatic antishock garments was recorded as well.

■ **TABLE 1** Baseline Patient Characteristics (Mean  $\pm$  SD)

	Mannitol ( <i>n</i> = 20)	Placebo ( <i>n</i> = 21)	p-value
Age	29 $\pm$ 12 years	27 $\pm$ 8 years	0.62
Pulse	99.5 $\pm$ 23.0 beats/min	105.0 $\pm$ 18.0 beats/min	0.41
Systolic blood pressure	124 $\pm$ 47 mm Hg	123 $\pm$ 32 mm Hg	0.80
Interval from trauma until initiation of study infusion	66 $\pm$ 30 min	66 $\pm$ 47 min	0.96
No. flown directly from injury scene	17 (85%)	19 (90%)	0.59
No. with initial systolic blood pressure <90 mm Hg	6 (30%)	3 (14%)	0.22
Volume IV fluid administered prior to flight team arrival	700 $\pm$ 730 mL	748 $\pm$ 659 mL	0.83
No. with >1 L IV fluid prior to flight team arrival	3 (14%)	4 (19%)	0.73
No. with pneumatic antishock garment inflated prior to flight team arrival	4 (20%)	4 (19%)	0.94
No. with blood administered prior to flight team arrival	1 (5%)	0 (0%)	0.30
Glasgow Coma Scale score	7.1	6.4	0.43
No. men	19 (95%)	20 (95%)	0.97
No. intubated prior to flight team arrival	9 (45%)	14 (70%)	0.16
No. with ethanol >0 mg/dL [ $>0$ mmol/L]	6 (30%)	5 (24%)	0.65
Ethanol level for those with ethanol present	189 $\pm$ 45 mg/dL [41 $\pm$ 10 mmol/L]	167 $\pm$ 51 mg/dL [36 $\pm$ 11 mmol/L]	0.22

Other data collected by chart review included whether the patient survived to hospital discharge, ICP monitoring data, and other neurologic procedures and diagnostic tests performed. Injury Severity Scale (ISS) scores using the AIS-90 classification were calculated by an experienced trauma registrar, based on injuries discovered during the patient's hospitalization or autopsy.<sup>10</sup> The TRISS method was used to predict the probability of survival.<sup>11</sup>

### Data Analysis

The treatment groups were compared for baseline parameters, as well as primary and secondary endpoints. The primary study endpoint was the change in systolic BP during the 2-hour observation period. Secondary endpoints included a change in pulse rate, the volume of IV solution administered, and urinary output.

■ **TABLE 2** Mechanism of Injury and Injury Severity

	Mannitol ( <i>n</i> = 20)	Placebo ( <i>n</i> = 21)
Mechanism		
Motor vehicle crash	11	16
Motorcycle crash	2	2
Pedestrian struck	3	1
Gunshot wound	2	1
Other	2	1
Injury Severity Scale score (median)	25	25
Abbreviated Injury Scale score (median)		
Head/neck	3.5	4.0
Face	0.0	0.0
Thorax	0.0	0.0
Abdomen/pelvis	0.0	0.0
Extremity	2.0	2.0
External	0.0	0.0

Data were analyzed using the rank sum test, Fisher's exact test, analysis of variance (ANOVA), and Dunnett's multirange test. All statistical tests were 2-tailed. Statistical comparisons were performed using Statistix 3.5 (Analytical Software, St. Paul, MN), JMP Statistical Software 2.0.5 (SAS Institute, Inc., Cary, NC), and Microsoft Excel 5.0 (Microsoft Corp., Redmond, WA). An  $\alpha < 0.05$  was considered significant.

### RESULTS

A total of 44 patients were enrolled in the study. However, 3 patients were excluded from analysis for the following reasons: the study solution infusion was discontinued by the attending emergency physician prior to completion because he did not believe that the patient had a head injury ( $n = 1$ ); the patient received a dose of furosemide prior to enrollment ( $n = 1$ ); and the patient was found to have had a hemorrhagic stroke rather than a head injury ( $n = 1$ ). The latter patient was found unresponsive in her vehicle after a minor traffic collision. She was taken to an outlying hospital and then transferred to the trauma center. Because of her depressed mental status with a GCS score of 3, she was assumed to have a head injury and was entered into the study. This patient received normal saline. After arrival at the trauma center, a CT scan of the brain revealed that she had an intracerebral hemorrhage consistent with a spontaneous bleed. No injury was identified.

All the patients who were not intubated before flight team arrival were intubated prior to administration of the study fluid. Of the remaining 41 patients, 20 received mannitol and 21 received placebo. The groups were similar with regard to age and baseline pulse, systolic BP, and GCS score (Table 1). No difference was found between the mannitol and placebo groups in overall ISS

score or head injury severity as measured by the injury scale for head and neck (Table 2). Mortality was 25% in the mannitol group and 14% in the placebo group ( $p = 0.38$  by Fisher's exact test). Table 3 describes the types of head injuries found in the enrolled patients.

The systolic BP did not change significantly during the 2-hour observation period (Fig. 1). Two hours after hospital arrival, systolic BP was lower in the mannitol group than in the placebo group ( $116 \pm 24$  mm Hg vs  $142 \pm 25$  mm Hg,  $p < 0.003$ ). However, when all time periods (including baseline values) were compared using ANOVA, there was no overall difference in systolic BP between the mannitol and placebo groups. There were 6 patients in the mannitol group and 3 patients in the control group who were hypotensive, with systolic BPs  $< 90$  mm Hg at the time of entry into the study. Figure 2 details the courses of these 9 patients during the observation period. Two initially hypotensive patients in both the mannitol and the placebo groups died.

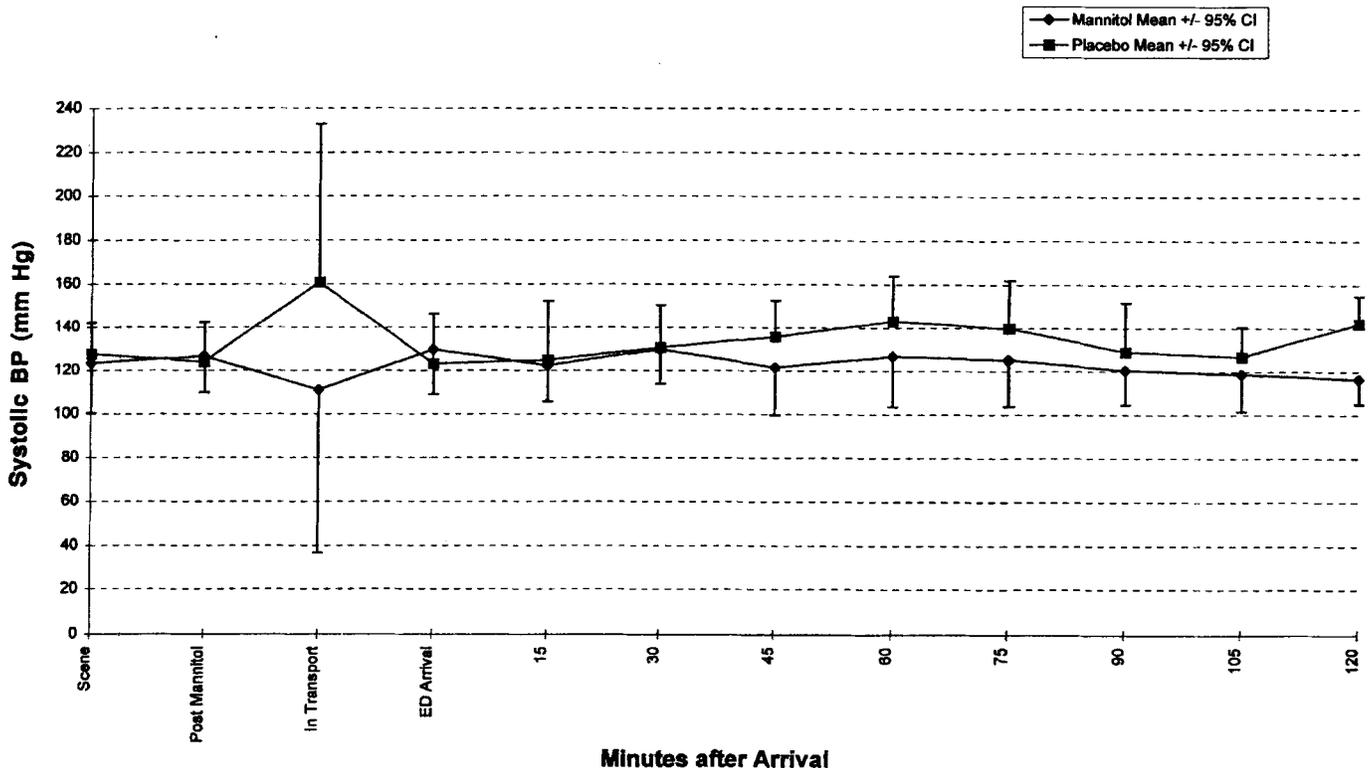
The patients' pulse rates did not change significantly, and there was no difference found between the mannitol and placebo groups at any time (Fig. 3). There was no difference in study volume administered to the groups: the mannitol patients received  $428 \pm 61$  mL and the placebo patients received  $410 \pm 73$  mL of study fluid. Overall, the mannitol patients received  $4,360 \pm 4,520$

■ TABLE 3 Types of Head Injuries Found in Enrolled Patients

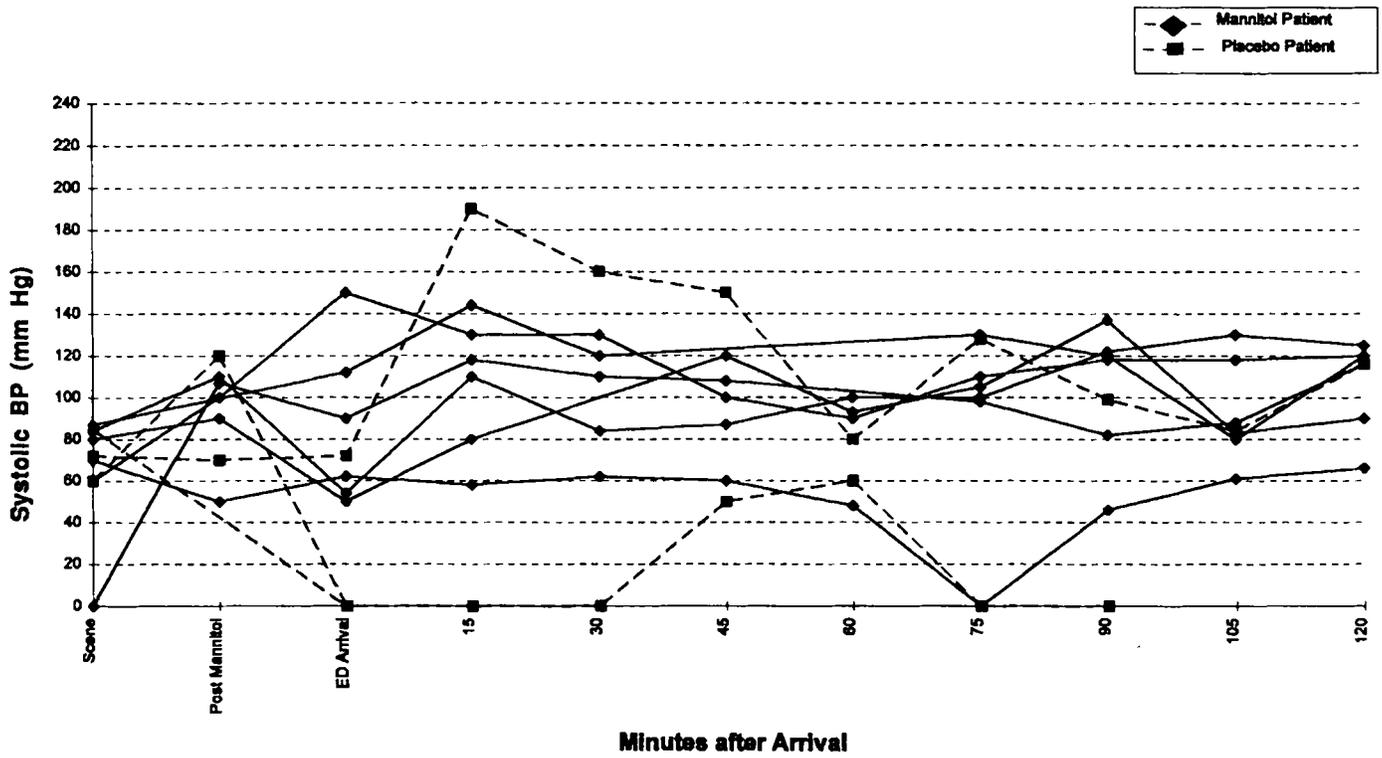
Injury	Mannitol (n = 20)	Placebo (n = 21)
Gunshot wound	2	1
Brain contusion or hemorrhage	8	6
Concussive injury without fracture	5	8
Intracranial vascular injury	0	2
Open skull fracture	1	1
Isolated closed skull fracture	1	1
Epidural hematoma	1	0
No brain injury found	2	2
Number with operative neurosurgical procedures	2	2

mL of IV fluid over the 2 hours, while the control patients received  $2,530 \pm 1,110$  mL of IV fluid ( $p = 0.20$ ) (Fig. 4). The variance in overall volume administered was significantly greater for the mannitol group ( $F = 16$ ,  $p < 0.001$ ). This large variance is due in part to 1 patient in the mannitol group who received 17,500 mL of IV fluid (including 6 units of blood) for ongoing hemorrhage, while having a urine output of only 15 mL over the 2-hour monitoring period.

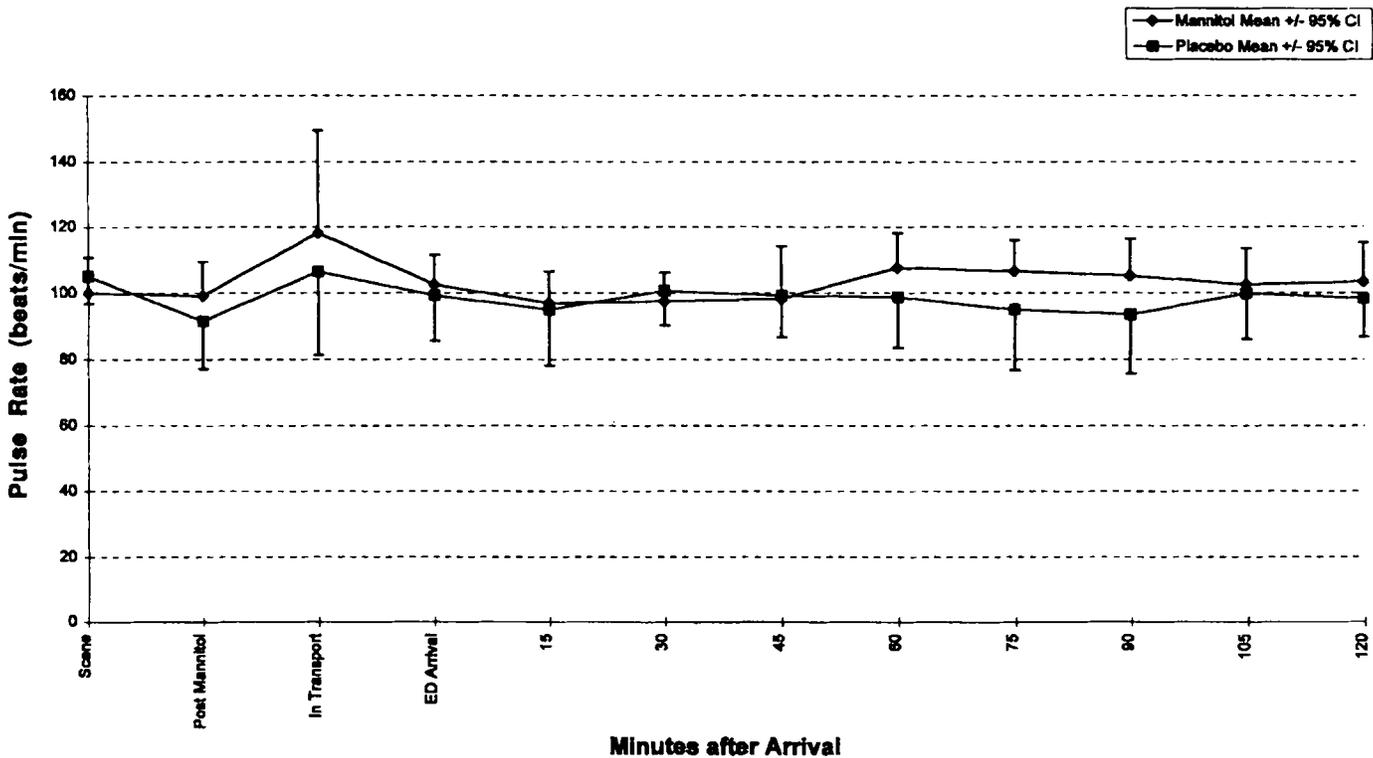
Urine output was  $1,351 \pm 608$  mL and  $634 \pm 444$  mL in the mannitol and placebo groups, respectively ( $p < 0.001$ ). The osmotic effect of mannitol also was re-



■ FIGURE 1. Systolic blood pressure (BP) from first contact with the flight team through 2 hours after hospital arrival. Plotted values are means, and the error bars represent 95% CIs for the means.



■ FIGURE 2. Systolic blood pressure (BP) changes over the 2-hour observation period for the 9 patients who had a systolic BP <90 mm Hg when first contacted by the flight team.



■ FIGURE 3. Pulse rate from first contact with the flight team through 2 hours after hospital arrival. Plotted values are means, and the error bars represent 95% CIs for the means.

flected in the patients' electrolyte levels. On hospital arrival, serum sodium was  $130.6 \pm 5.8$  and  $139.1 \pm 2.1$  in the mannitol and placebo groups, respectively ( $p < 0.00001$ ). Serum osmolarity was calculated rather than measured in the laboratory. Eight (40%) of the patients in the mannitol group and 4 (19%) of the patients in the placebo group received blood transfusions after administration of the study fluid ( $p = 0.14$ ).

The patients were moderately hyperventilated on hospital arrival. Initial ABG analysis revealed the following values for the mannitol and placebo groups, respectively: pH  $7.30 \pm 0.16$  and  $7.33 \pm 0.18$ ;  $PO_2$   $298 \pm 148$  and  $327 \pm 193$  torr; and  $PCO_2$   $34 \pm 7.5$  and  $33 \pm 11$  torr. There was no statistically significant difference between the groups.

Using the TRISS methodology, both groups had better than expected outcomes, although the distribution of ISS scores did not match the Major Trauma Outcome Study (MTOS) norms.<sup>11</sup> The mannitol group Z-score was  $-2.6$ ; and the placebo group Z-score was  $-3.4$ .

A post-hoc power analysis was performed. Using the means and SDs found in the study sample, there was an 83% chance of detecting a fall in mean systolic BP to  $<90$  mm Hg.

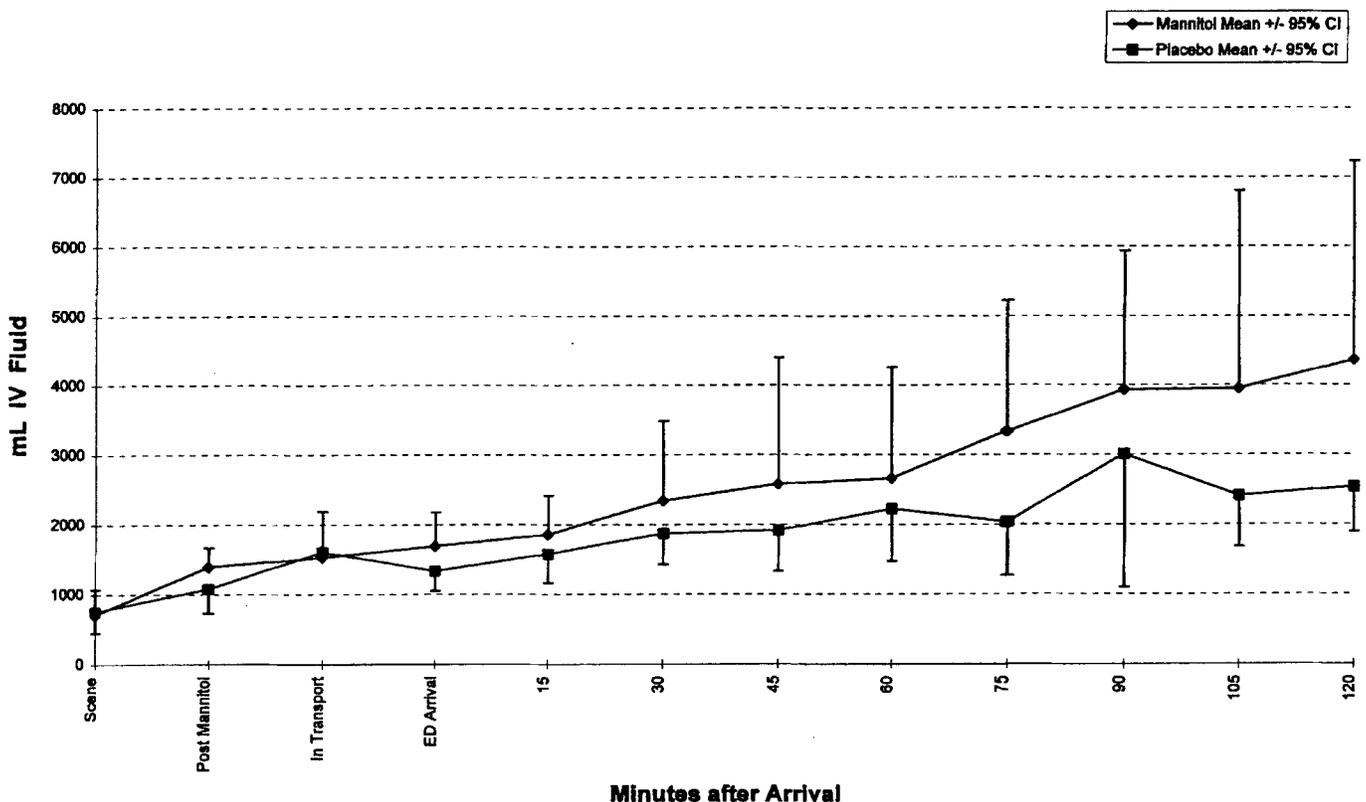
During the 2-hour monitoring period, the treating physicians requested that the identity of the study fluid

be unblinded for 2 patients (11%) who had received mannitol and 3 patients (15%) who had received placebo.

At the conclusion of the 2-hour monitoring period, the EM resident and the investigator recording the patient data were asked to provide their guesses as to whether mannitol or placebo had been administered to the patient. For those patients actually given mannitol, the resident correctly picked mannitol in 11 of 13 cases for which a guess was given; and the investigators correctly picked mannitol in 13 of 14 cases. For those patients actually given placebo, the resident correctly picked placebo in 5 of 10 cases for which a guess was given; and the investigators correctly picked placebo for 13 of 16 cases.

## DISCUSSION

Mannitol has been shown to have a number of effects that are likely to be beneficial in the brain-injured patient. Its precise mechanism of action is unclear, but it is likely more complex than simply lowering ICP by dehydrating brain tissue. Mannitol may have a cerebro-protective effect by limiting secondary ischemic injury,<sup>12</sup> and it may improve cerebral perfusion by decreasing blood viscosity.<sup>13,14</sup> Mannitol also may decrease the for-



■ FIGURE 4. IV fluid volume administered from first contact with the flight team through 2 hours after hospital arrival. Plotted values are means, and the error bars represent 95% CIs for the means.

mation of cerebrospinal fluid.<sup>15</sup> It is clear that administration of mannitol carries some risk of adverse effects such as acute renal failure,<sup>16</sup> and transient hypotension lasting <5 minutes has been reported after very rapid administration of mannitol in the operating suite.<sup>17</sup> Multiple doses of mannitol may actually increase water content in injured cerebral tissues because the blood-brain barrier is disrupted.<sup>18</sup>

Few studies have examined the use of mannitol prior to hospital arrival of the head-injured patient. We attempted to examine the safety of out-of-hospital administration of mannitol in multiply injured patients with head injuries. Data from this pilot investigation suggest that out-of-hospital mannitol administration does not significantly change systolic BP in head-injured multiple-trauma patients. There is an insufficient number of patients in this pilot study to assess whether out-of-hospital mannitol administration to head-injured patients with other concomitant injuries is beneficial overall.

This investigation was initiated because some physicians have expressed concern that empiric administration of IV mannitol may adversely affect a trauma patient's hemodynamic status. Specifically, they suggest that mannitol administration may cause hypotension and further compromise cerebral perfusion.<sup>5</sup>

Based on this concern, many centers administer mannitol only after directly measuring ICP. However, in a study designed to assess the impact of ICP monitoring on outcome from severe head injury, no difference in outcome was found between ICU patients receiving empiric mannitol and those receiving mannitol only for documented ICPs > 25 mm Hg.<sup>19</sup> Since there was not a placebo control in that study, it is unknown whether mannitol administration was detrimental or beneficial for both those patients with very high ICPs and those with lesser degrees of ICP elevation. If mannitol were of benefit for patients with mild elevations in ICP, a more liberal policy of mannitol administration would be generally beneficial.

It is commonly taught that mannitol should be given only when hyperventilation has been tried and failed to produce the desired reduction in ICP.<sup>20</sup> However, there is evidence that prolonged hyperventilation is harmful and that relative normocapnia such as found in our patients is desirable.<sup>21,22</sup>

Animal research suggests that mannitol administration improves hemodynamic parameters. In a dog model of concomitant increased ICP and hemorrhagic shock, administration of mannitol significantly decreased ICP while simultaneously increasing mean arterial pressure (MAP).<sup>23</sup> Other animal hemorrhage studies also have demonstrated that mannitol administration increases BP, although, unlike solutions containing dextran 70, the hypertensive effect is not maintained.<sup>24-26</sup> Our data support the conclusions of these animal studies that mannitol

does not have an adverse effect on systemic hemodynamic parameters such as systolic BP or pulse rate.

Mannitol administration in an ICU setting does not appear to adversely effect hemodynamics.<sup>27</sup> In a study of 16 ICU patients with elevated ICPs, Rosner and Coley demonstrated that when cerebral perfusion pressure (CPP) was compromised (<70 mm Hg), administration of mannitol resulted in an increase in MAP, a decrease in ICP, and an improvement of CPP. For patients with CPPs >70 mm Hg, mannitol was found to have little effect on any hemodynamic parameter.<sup>28</sup>

Because empiric administration of mannitol to ICU patients does not appear to be harmful and because others have found evidence for improved outcome when mannitol and endotracheal intubation were used,<sup>29</sup> a policy of empiric mannitol administration in the out-of-hospital setting to trauma patients with evidence for head injury might be beneficial. The purpose of our study was to test whether empiric out-of-hospital administration of mannitol was safe, before proceeding with a future trial to demonstrate efficacy.

This study demonstrated that out-of-hospital administration of mannitol to trauma patients with abnormal GCS scores did not adversely change systolic BP. During the observation period, there was no significant difference from baseline in either the mannitol or the placebo group. Supporting evidence that there was no significant hemodynamic effect is provided by the fact that there was no difference between the mannitol and the control groups' pulse rates during the observation period.

## ■ LIMITATIONS AND FUTURE QUESTIONS

Before application of the results of this study, its limitations must be considered. First, the study was not designed to detect differences in mortality rates. Given the overall mortality rate of 20%, 1,447 patients would be needed in each group to detect an absolute mortality difference of 4%.

Second, some might argue that the most sensitive hemodynamic parameter to follow in trauma patients is the diastolic BP. In both out-of-hospital care and ED care of these unstable trauma patients, BP was frequently measured using palpation techniques or Doppler stethoscopes. Therefore, the diastolic BP was not regularly obtained. Systolic BP is currently the most practical and frequently followed hemodynamic parameter in out-of-hospital and ED trauma patients.

Third, this study was limited by the fact that we included patients with blunt and penetrating head injuries. Penetrating-head-injury patients with GCS scores of 3 have essentially 100% mortality, and these patients probably should be excluded from future investigations. A reanalysis of the data with the 3 penetrating trauma pa-

tients excluded reveals a mortality rate of 17% vs 10% (mannitol vs control).

Some readers might question the dose of mannitol used for the study. Mannitol usually is administered in doses from 0.25 g/kg to 1.0 g/kg. In a study by Marshall et al., a dose of 0.25 g/kg produced the same reduction in ICP as did higher doses.<sup>30</sup> In contrast, Roberts et al. demonstrated a dose-dependent effect of mannitol on ICP reduction.<sup>31</sup> Other studies suggest that a higher mannitol dose is needed to elevate cardiac output and BP (e.g., 0.5 g/kg,<sup>32</sup> 0.72 g/kg,<sup>24</sup> 1.0 g/kg,<sup>28</sup> and 2.0 g/kg<sup>23</sup>). Because it is unclear how much mannitol is needed to produce maximal reduction in ICP and because higher doses of mannitol appear to elevate MAP under some circumstances, a dose of 1.0 g/kg was chosen for use in this trial in hopes of empirically optimizing CPP.

Nine patients in this study were hypotensive at the time of enrollment. However, as demonstrated in Figure 2, no consistent effect on systolic BP was seen for these patients. Of note, 2 (both control patients) did not survive the 2-hour observation period. A larger study of initially hypotensive patients is warranted, especially in light of recent animal evidence that administration of hypertonic fluids may improve hemodynamics in head injury with concomitant hemorrhagic shock,<sup>33</sup> and in light of recent clinical data that normal saline administration to victims of penetrating torso trauma is not beneficial.<sup>34</sup>

## CONCLUSION

Out-of-hospital administration of 1.0 g/kg of mannitol to the multiple-trauma patient with head injury is not associated with any significant change in systolic BP or pulse rate. Before routine out-of-hospital administration of mannitol to all head-injured, multiple-trauma patients can be recommended, larger clinical trials are needed to determine the effect on neurologic outcome and mortality.

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### Further Thoughts from the Reviewers

■ This study was designed and executed in 1991-1992 with the intent of answering an important question for emergency physicians. At the time this study was conducted, many clinicians gave mannitol to all patients with serious head injuries. The potential hypotensive effects of mannitol, especially in

patients with multiple trauma, represented a significant clinical concern.

In December 1995, the American Association of Neurological Surgeons (AANS) advanced a series of guidelines for the treatment of the severely traumatized head-injured patient. The AANS advocates the use of mannitol in circumstances in which the patient has signs of increased ICP or signs of deteriorating neurologic status. By these new guidelines, mannitol would not be given routinely to all patients with serious head trauma.

At the time this study was conducted, resuscitation research was frequently performed with a waiver of informed consent or "deferred" consent. Resuscitation research had been performed for many decades using these consenting mechanisms, since the U.S. regulatory research guidelines did not address circumstances in which patients would be too critically ill or injured to provide prospective informed consent. Since 1993, deferred consent has been disallowed by the Office for the Protection from Research Risks. A more stringent interpretation of regulatory guidelines also has made it quite difficult to apply a waiver of prospective informed consent in resuscitation research. This is problematic since patients are unable to speak for themselves, and often no legally authorized representative can be found. As resuscitation researchers know, it has become nearly impossible to investigate potentially promising new therapies in the acute or critical care setting because of these regulatory restrictions. Based on the input from the resuscitation research community, the FDA and the NIH are currently developing new guidelines that should allow resuscitation research in the setting where prospective informed consent is not possible.

This study may seem outdated given the current guidelines for mannitol administration. However, the study results provide important hemodynamic data relevant to those out-of-hospital multiple-trauma patients with head injuries who do warrant mannitol administration. Clearly, mannitol administration is unlikely to produce significant hemodynamic deterioration.